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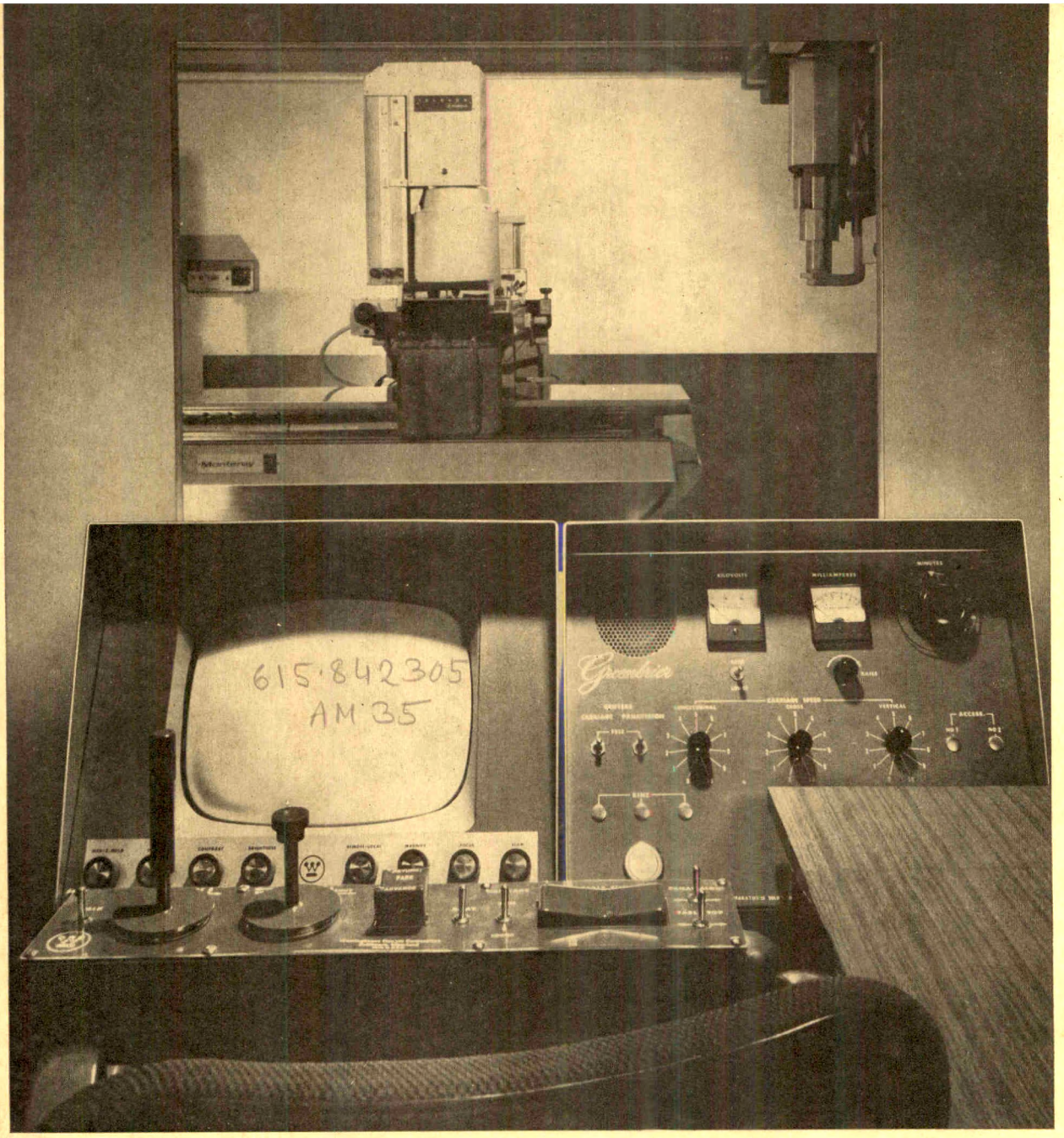
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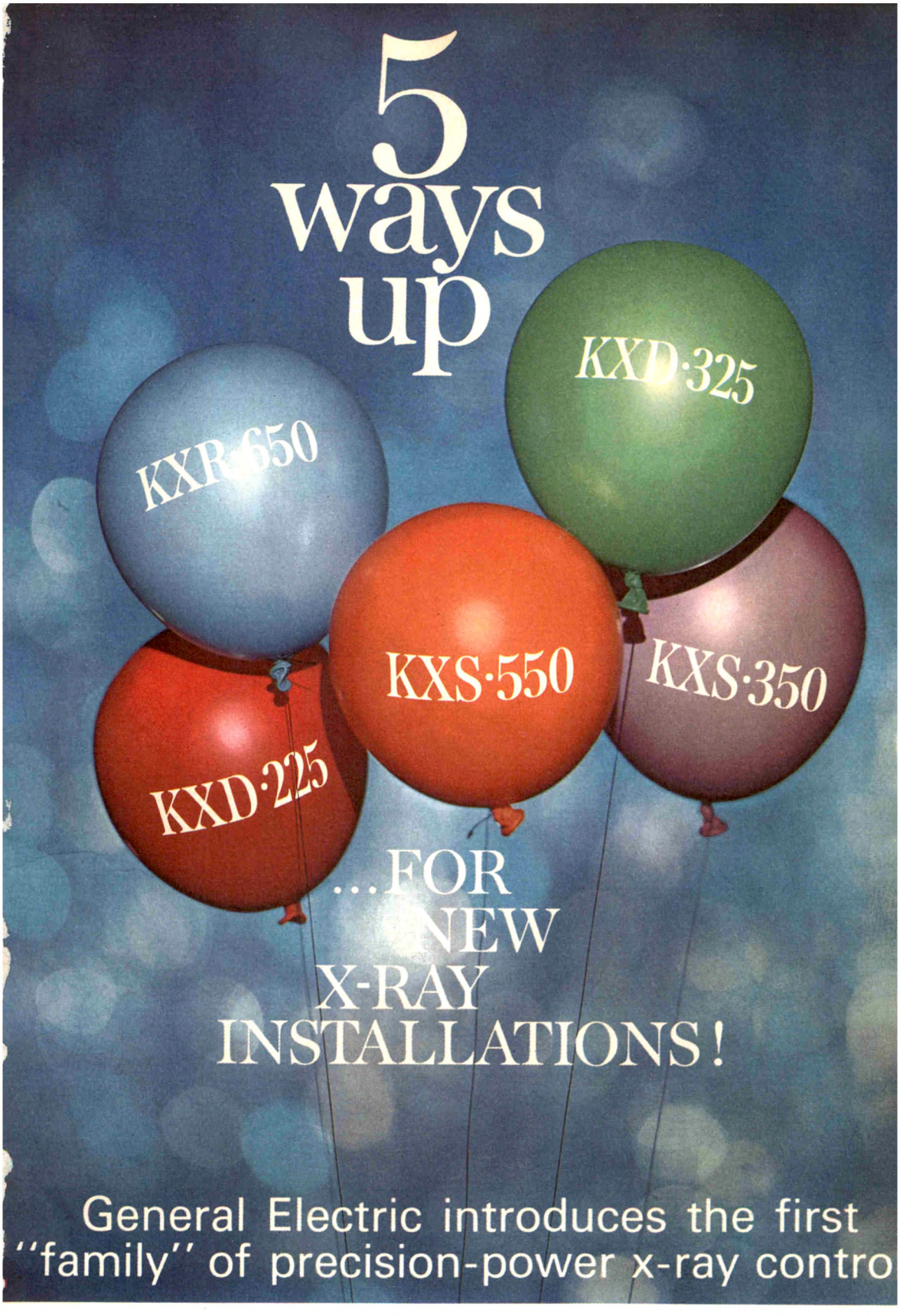
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New – for same-day oral cholangiography and cholecystography, even in unprepared patients.



Oragrafin permits rapid or routine cholangiography and cholecystography in prepared and unprepared patients and is particularly suitable in geriatric,[6] cardiac,[6] and obese[4] patients. Oragrafin is available as Oragrafin Calcium and Oragrafin Sodium. Oragrafin Calcium Granules permit flexibility in dosage and may be used for both over-night and same-day visualization; Oragrafin Sodium Capsules are intended for over-night radiography. Optimal concentration of either salt in the hepatic or biliary ducts occurs 1-3 hours after ingestion in nearly all cases.[1,2] Diagnostically significant filling of the gallbladder takes place within 5 hours or less after ingestion,[1,2] particularly with Oragrafin Calcium.

Oragrafin causes few side effects:[3,5] Oragrafin Sodium and Oragrafin Calcium are usually well tolerated. Only 11 transient reactions were noted in a 300-patient study – "a very low incidence of side effects."[4] "Oragrafin was superior to [iopanoic acid] in causing a definite lesser incidence of diarrhea and cramping."[7]

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References: (1) Richter, K., and others: Deutsche Gesundh. *15*:630 (March 24) 1960. (2) Saltzman, G. F.: Acta radiol. *54*:417 (Dec.) 1960. (3) Whiteside, C. G.: Brit. J. Radiol. *33*:124 (Feb.) 1960. (4) Brannan, H. M., and others: Proc. Staff Meet. Mayo Clin. *36*:197 (April 12) 1961. (5) Kemp, F. H., and Wright, F. W.: Brit. J. Radiol. *34*:63 (Jan.) 1961. (6) Saltzman, G. F., and Sundstrom, K. A.: Acta radiol. *54*:353 (Nov.) 1960. (7) White, W. W., and Fischer, H. W.: Am. J. Roentgenol. *87*:745 (April) 1962.

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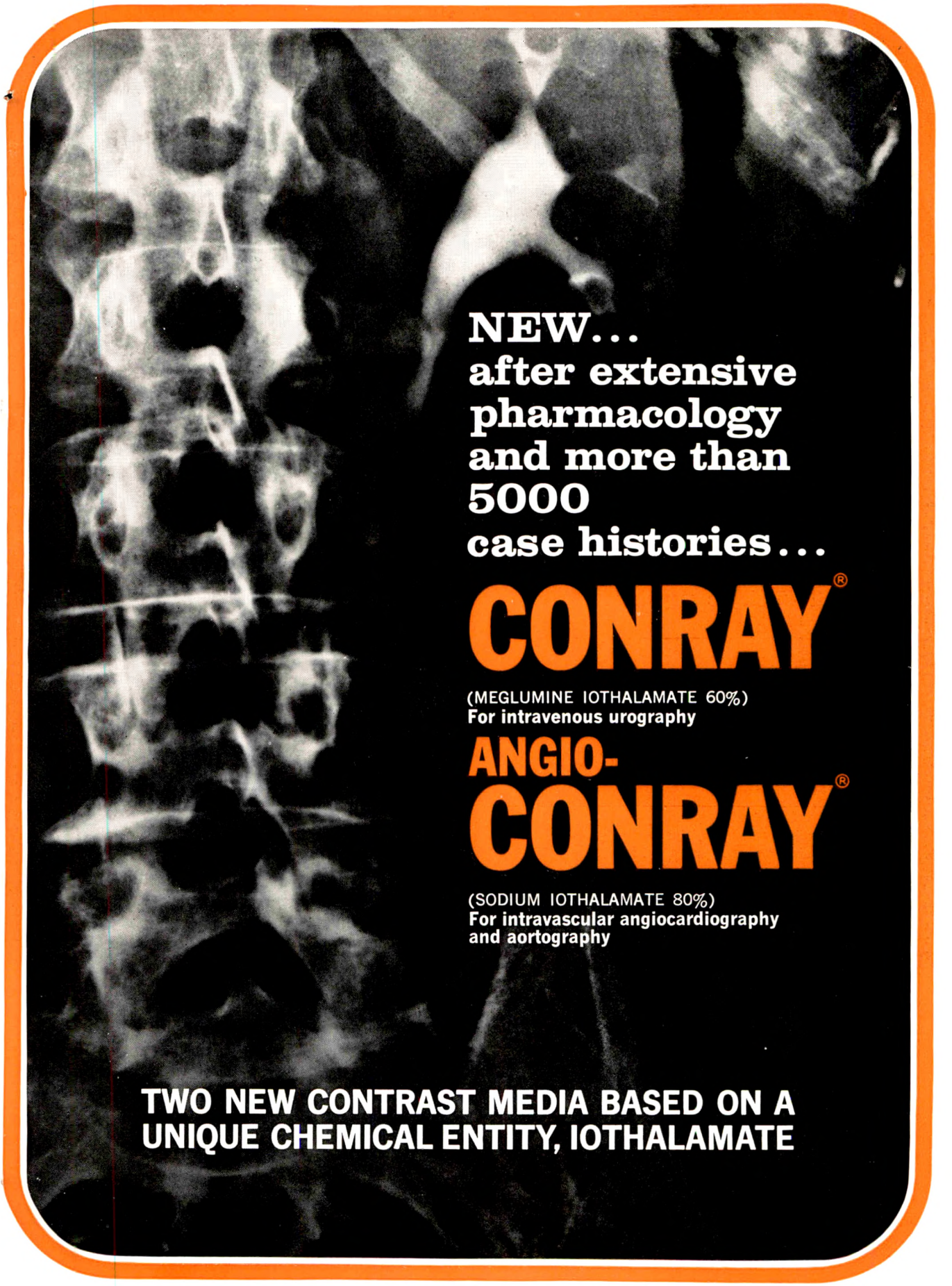
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after extensive
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CONRAY®
(MEGLUMINE IOTHALAMATE 60%)
For intravenous urography
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CONRAY®
(SODIUM IOTHALAMATE 80%)
For intravascular angiocardiography
and aortography
TWO NEW CONTRAST MEDIA BASED ON A
UNIQUE CHEMICAL ENTITY, IOTHALAMATE

Pharmacological findings:

A high degree of safety has been demonstrated by the extensive pharmacology conducted on CONRAY and Angio-CONRAY, both salts of the same new compound, iothalamic acid. No attempt is made to summarize all findings here . . . only some important data are presented. A complete bibliography appears on the following pages.

INTRACORONARY INJECTIONS IN DOGS

"Increasing-dose, alternate-injection studies in our laboratory revealed that in dogs there were fewer electrocardiographic changes associated with the intracoronary delivery of /iothalamate/ than diatrizoate." [1]

INTRA-AORTIC INJECTIONS IN DOGS

Neurologic responses [2]

	Number of Dogs	Immediate Neurologic Response	Post-Anesthetic Findings			
			Neurologic:		Renal:	
			Paresis	Paraplegia	Azotemia	Necrosis
Sodium iothalamate 80% (Angio-CONRAY)	20	0	0	0	0	0
Sodium and methylglucamine diatrizoates 90%	30	43%	7%	0	0	0

Histological examination of kidneys . . .

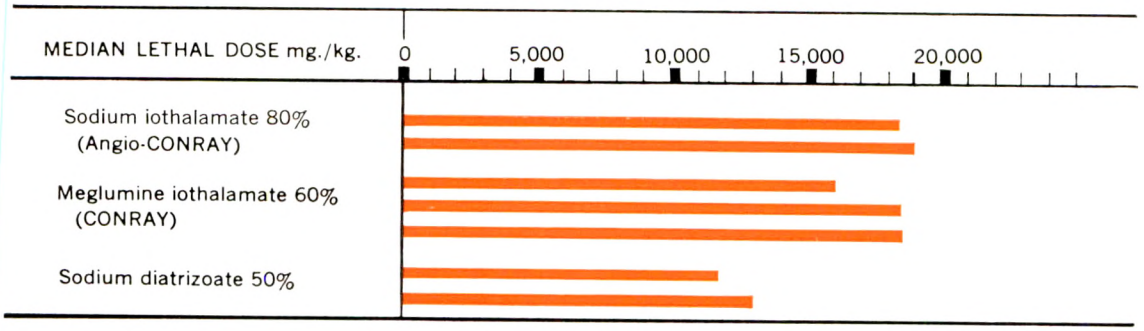
following intra-aortic injection of large doses of iothalamate.

"Microscopic sections of both kidneys of all the dogs /10/ were entirely within normal limits. Specifically, there was no evidence of glomerular destruction, tubular damage, casts, or vascular pathology." [4]

Pharmacological findings: (cont'd)

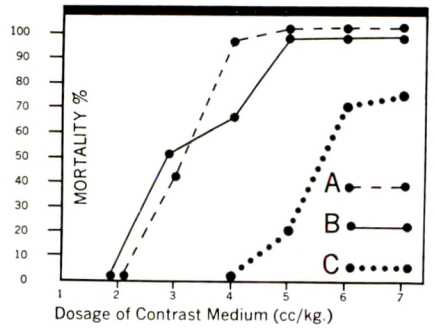
ACUTE TOXICITY

Intravenous LD_{50} in mice[9]



In achieving the acute lethal range in mice and rats, the total volume of undiluted iothalamate solutions administered intravenously *was almost equivalent to the estimated total blood volumes of these animals.* [9]

Intravenous injections in dogs [2,15]



A SODIUM ACETRIZOATE 70%

B SODIUM AND METHYLGLUCAMINE DIATRIZOATES 90%

C [Angio] CONRAY 80%

"Thus the margin of safety in intravenous injections was far greater with Angio-CONRAY." [2]

BLOOD BRAIN BARRIER STUDIES IN DOGS[9,14]

Using a modification of previously reported blood brain barrier tests (Broman and Olsson; Whiteleather; De Saussure), intracarotid injections were made in dogs using 25 cc. of meglumine iothalamate 60% and sodium diatrizoate 50% followed by infusion of Trypan blue dye.

	No. of Dogs	None	Barely Perceptible	Faint	Distinct	Intense
25 cc. meglumine iothalamate 60% (CONRAY)	14	4	3	6	1	0
25 cc. sodium diatrizoate 50%	11	0	0	2	3	6

Even more important than brain staining were the differences in neurological responses when the two media were injected. Dogs receiving sodium diatrizoate (11 dogs) exhibited numerous observable neurological responses such as strong contractions of the neck and thoracic muscles (7 dogs), clonicotonic convulsions and hypersensitivity to sound and touch (9 dogs).

Dogs receiving CONRAY exhibited no convulsions nor hypersensitivity to sound and touch. Four showed slight to mild contractions of the neck and thoracic muscles. The remaining 10 dogs appeared unaffected by the injections.

Clinical commentary:

IN OVER 5000 CASES, [1-3, 6, 7, 12-14, 16, 17]

there has been general agreement among investigators that patient tolerance with iothalamate has been better than that previously experienced with other available agents.

"...The intravenous injection of /CONRAY/ for urography is practically devoid of unpleasant reaction." **STEINBERG, I. and EVANS, J. A.**[16]

"In view of its several distinct advantages, it is likely that iothalamate will supersede presently available agents for cardiovascular contrast visualization." **STRAUBE, K. R. and DOTTER, C. T.**[17]

"At the present time, Angio-CONRAY would appear to be the concentrated angiographic medium of choice." Foster, et al. further state that "experimental studies clearly demonstrated that sodium iothalamate is the least toxic angiographic contrast medium yet tested." **FOSTER, J. H., et al.**[2, 3]

"If further clinical experience confirms our impression of its relative safety and freedom from side effects, /iothalamate/ will, in fact, warrant the term 'drug of choice'—at least until a better preparation is found." Citing the importance of the need for rapid delivery of concentrated contrast media through small bore catheters, Dotter, et al. further observed that "...from this point of view, /iothalamate/ is an outstanding medium." **DOTTER, C. T., et al.**[1]

"Clinical experience with a new concentrated contrast agent, Angio-CONRAY, in angiocardiography, nephrotomography, intravenous aortography, and retrograde renal arteriography indicates that the usual reaction was mild and transient, and was well tolerated. Low viscosity and ready solubility of Angio-CONRAY permit ease and speed of injection. These factors, together with good contrast visualization, make Angio-CONRAY a preferable contrast medium for angiographic procedures." **KANICK, V. and FINBY, N.**[7]

"Angio-CONRAY is the agent of choice for aortography and angiocardiography. CONRAY is the preferred agent for intravenous urography... It appears that the compound is more rapidly excreted than the other common opaques and maximum density of contrast is evident in five minutes." **MARSHALL, M. D. and LING, J. T.**[13]

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Physical characteristics:

Iothalamate is a new chemical entity synthesized and developed by Mallinckrodt Pharmaceuticals. It is chemically identified as 5-acetamido-2, 4, 6-triiodo-N-methylisophthalamate. CONRAY is an aqueous solution of meglumine iothalamate at 60% concentration. Angio-CONRAY is an aqueous solution of sodium iothalamate at 80% concentration.

Both in iodine content and viscosity, Angio-CONRAY is superior to comparable diatrizoates. It has the highest iodine content (48%) of any available contrast medium, and its viscosity is almost 3 times lower than comparable diatrizoates.



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at room temperature
and even below 32° F.

Angio-CONRAY
77° F.

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(MEGLUMINE IOTHALAMATE 60%)
For intravenous urography

ANGIO-CONRAY®

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For intravascular angiocardiography and aortography

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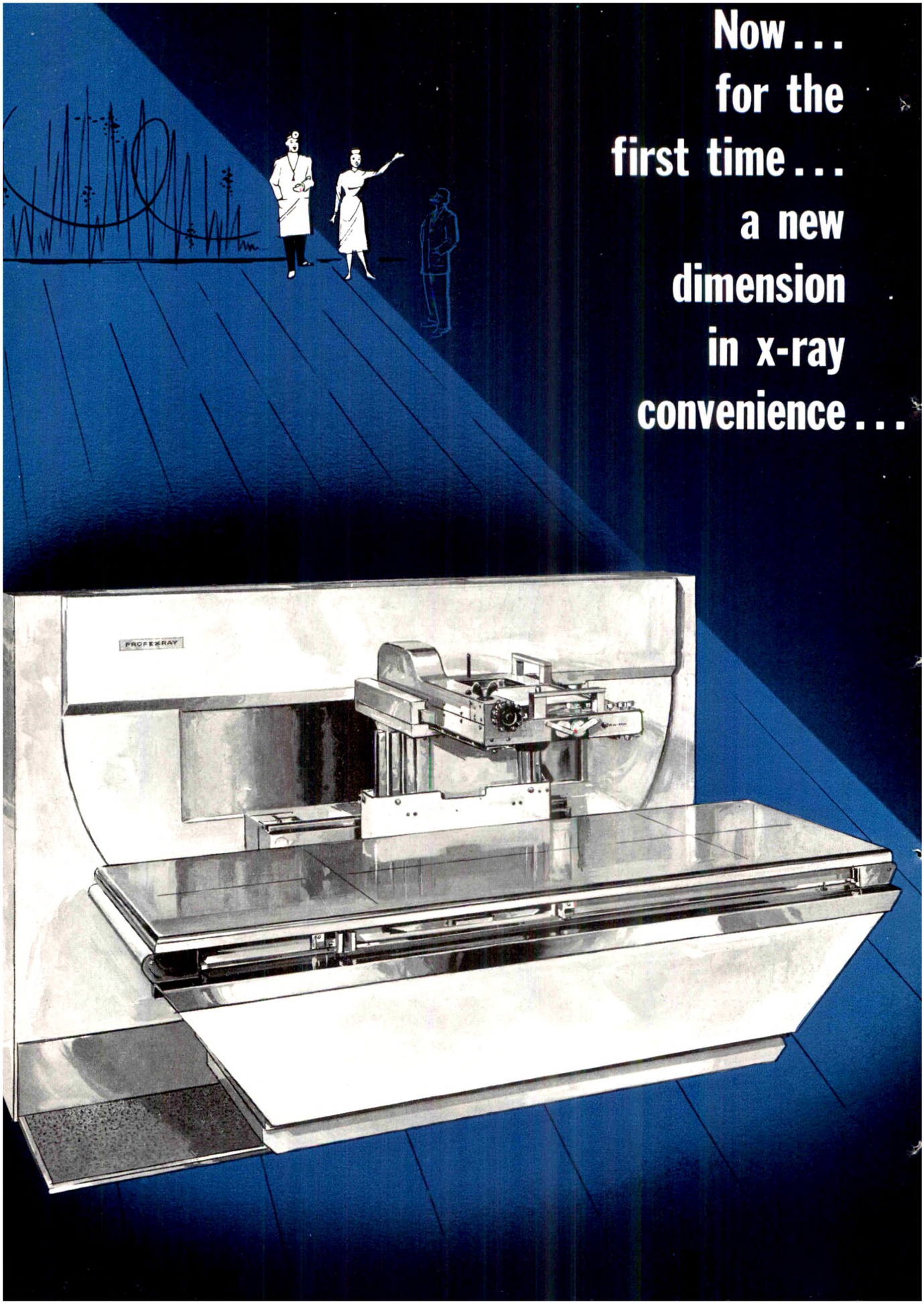

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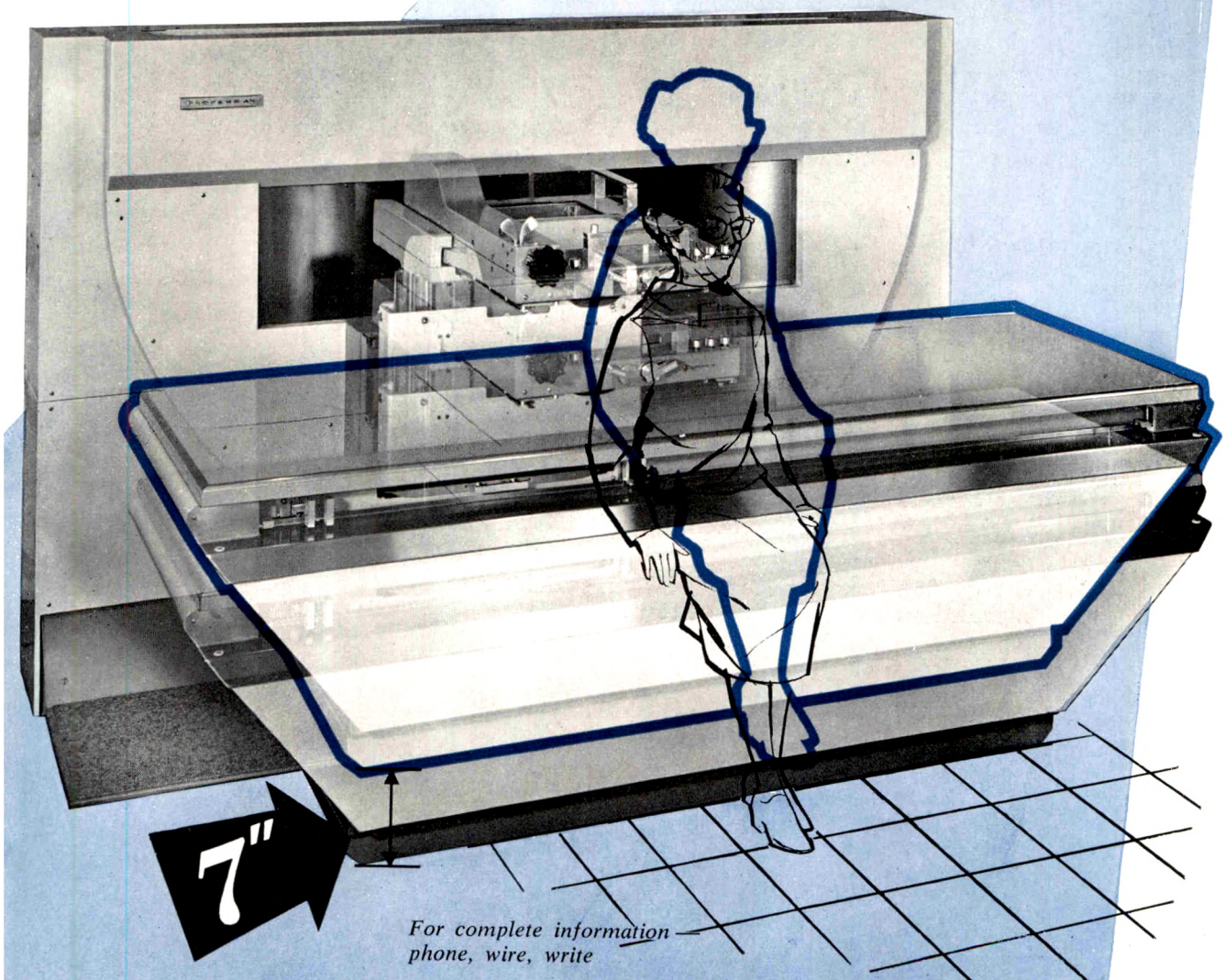
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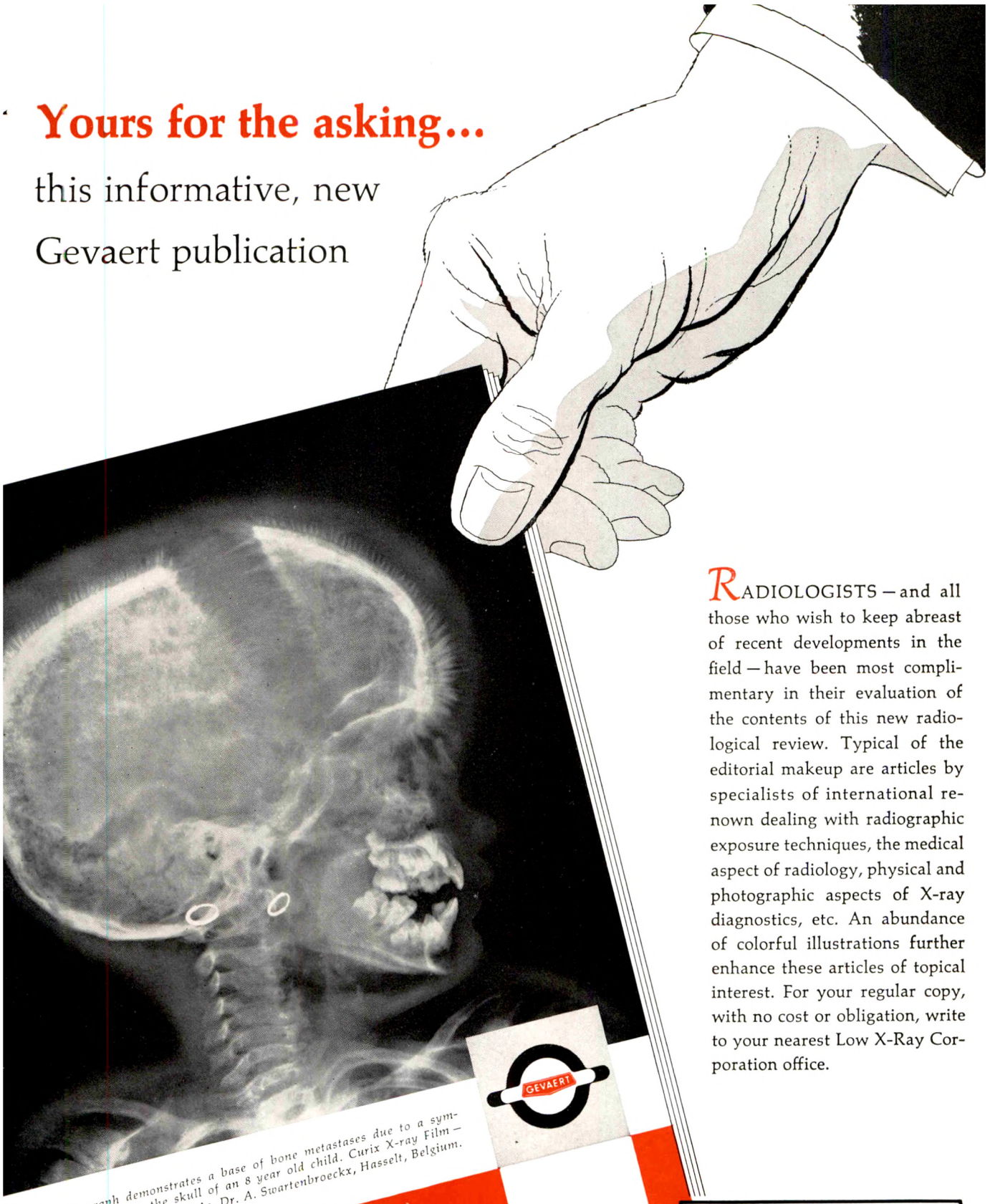
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This radiograph demonstrates a base of bone metastases due to a symphaticoblastoma, in the skull of an 8 year old child. Curix X-ray Film — 1 metre F.F.D.—56 kV—80 mAs. Dr. A. Swartenbroeckx, Hasselt, Belgium.

X-RAY BULLETIN

INTERNATIONAL REVIEW OF MEDICAL RADIOGRAPHY

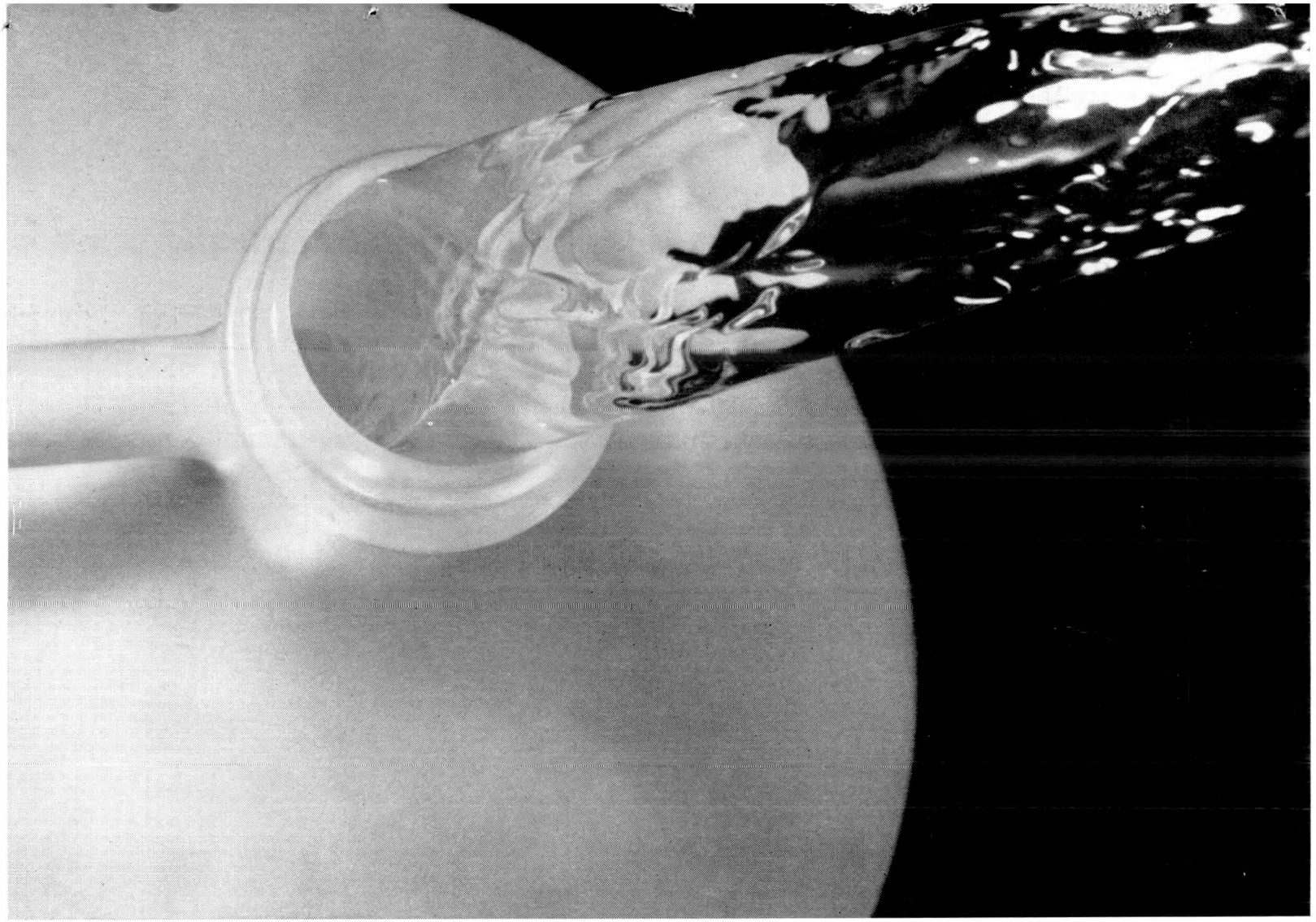
RADIOLOGISTS — and all those who wish to keep abreast of recent developments in the field — have been most complimentary in their evaluation of the contents of this new radiological review. Typical of the editorial makeup are articles by specialists of international renown dealing with radiographic exposure techniques, the medical aspect of radiology, physical and photographic aspects of X-ray diagnostics, etc. An abundance of colorful illustrations further enhance these articles of topical interest. For your regular copy, with no cost or obligation, write to your nearest Low X-Ray Corporation office.

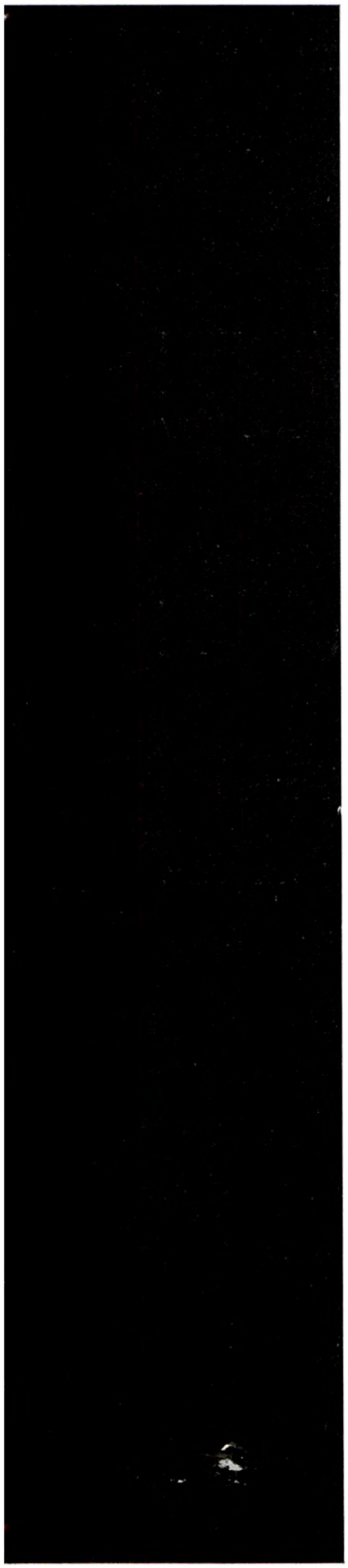
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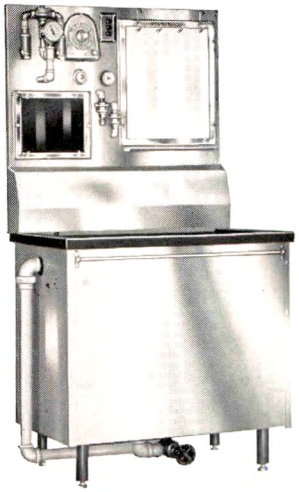
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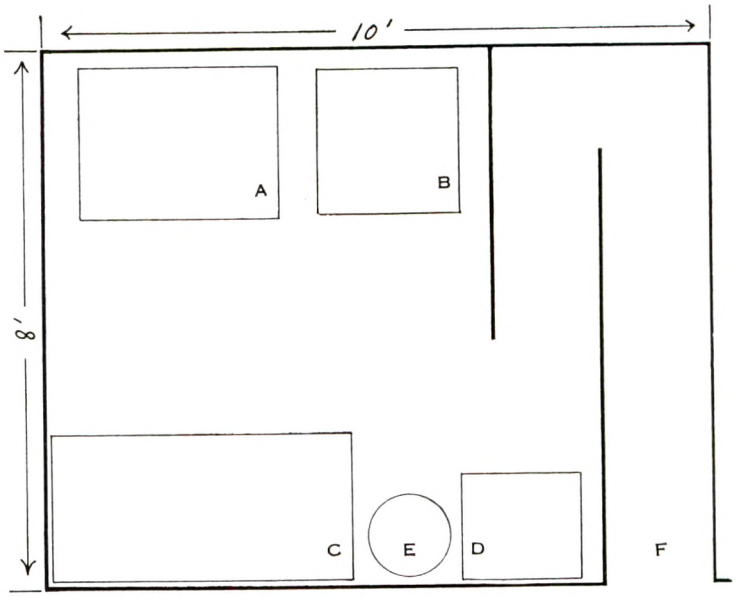
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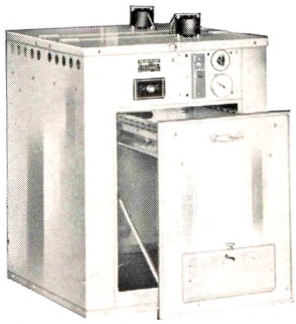


A--FL. SP., 26 X 36 IN.

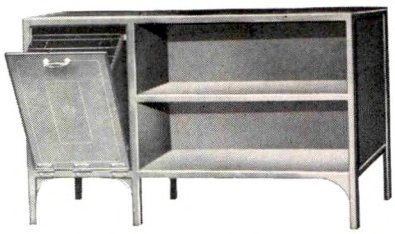


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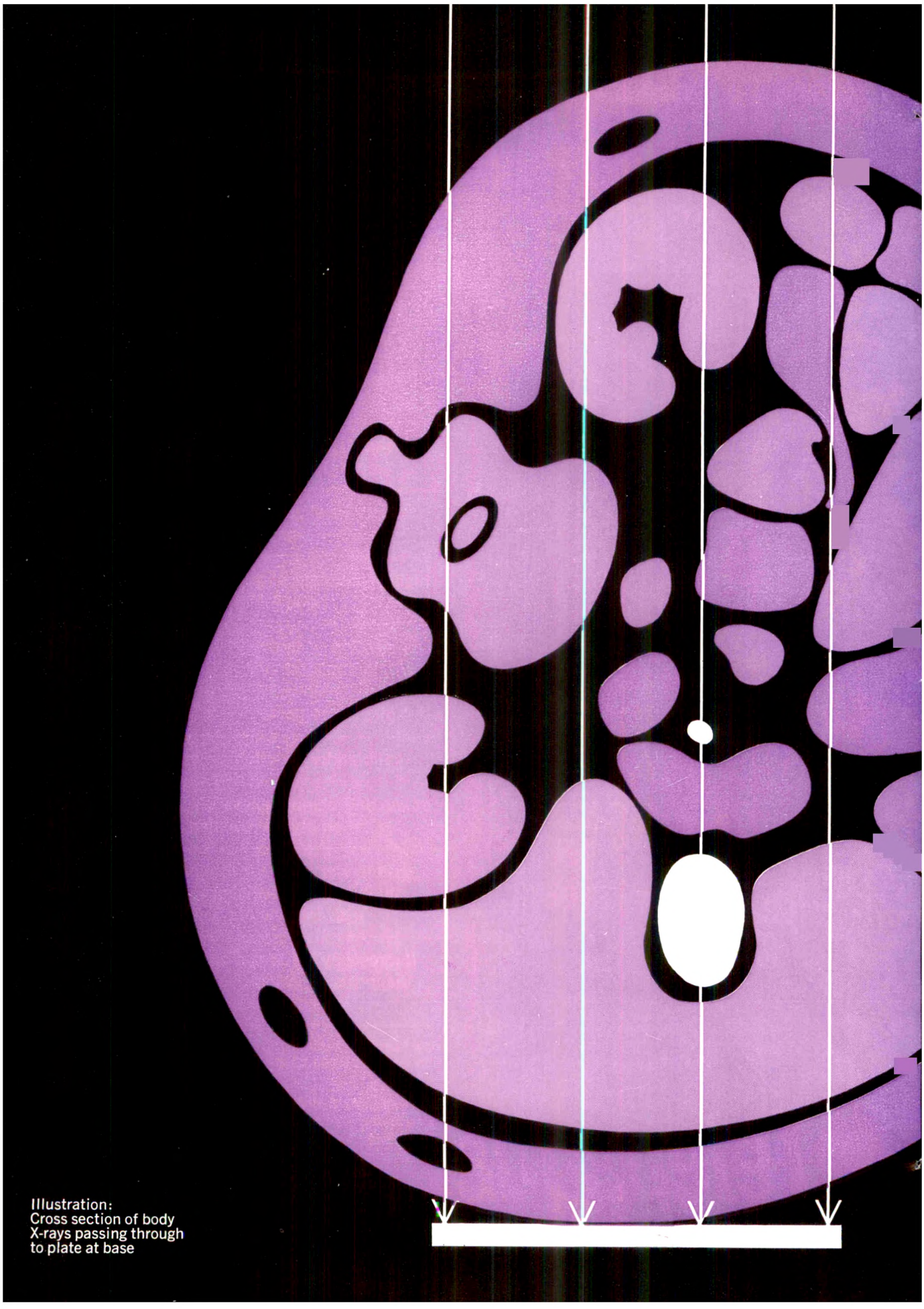


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1. Whitehouse, W. M.: Iopanoic acid, Ann. New York Acad. Sc. 78:809, July 2, 1959. 2. Baker, H. L., Jr., and Hodgson, J. R.: Further studies on the accuracy of oral cholecystography, Radiology 74:239, Feb. 1960.

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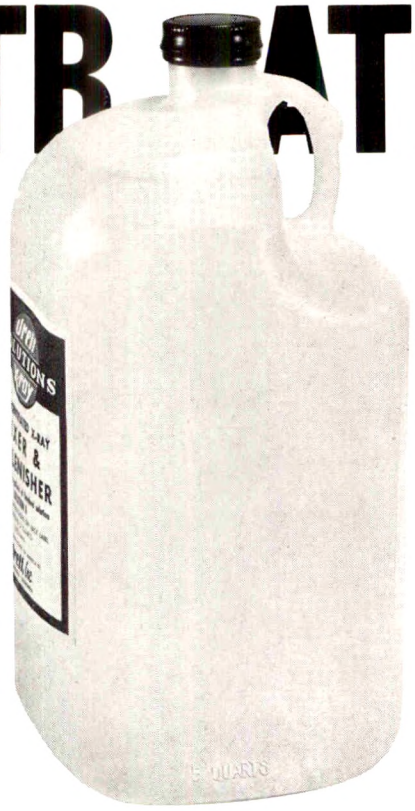
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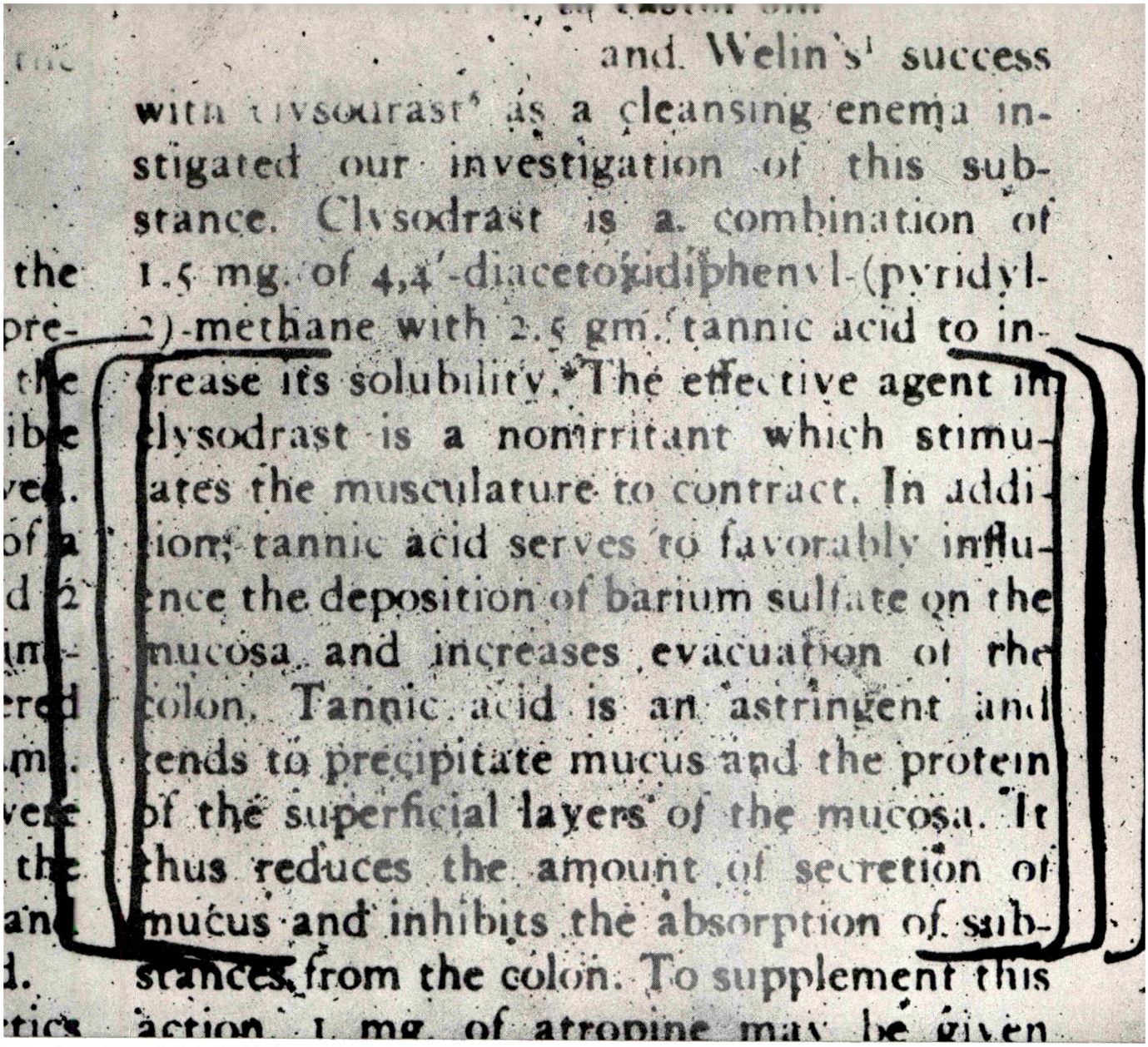
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Reference: Steinbach, H. L., and Burhenne, H. J.: Performing the Barium Enema: Equipment, Preparation, and Contrast Medium. Am. J. Roentgenol. 87:644, 1962.

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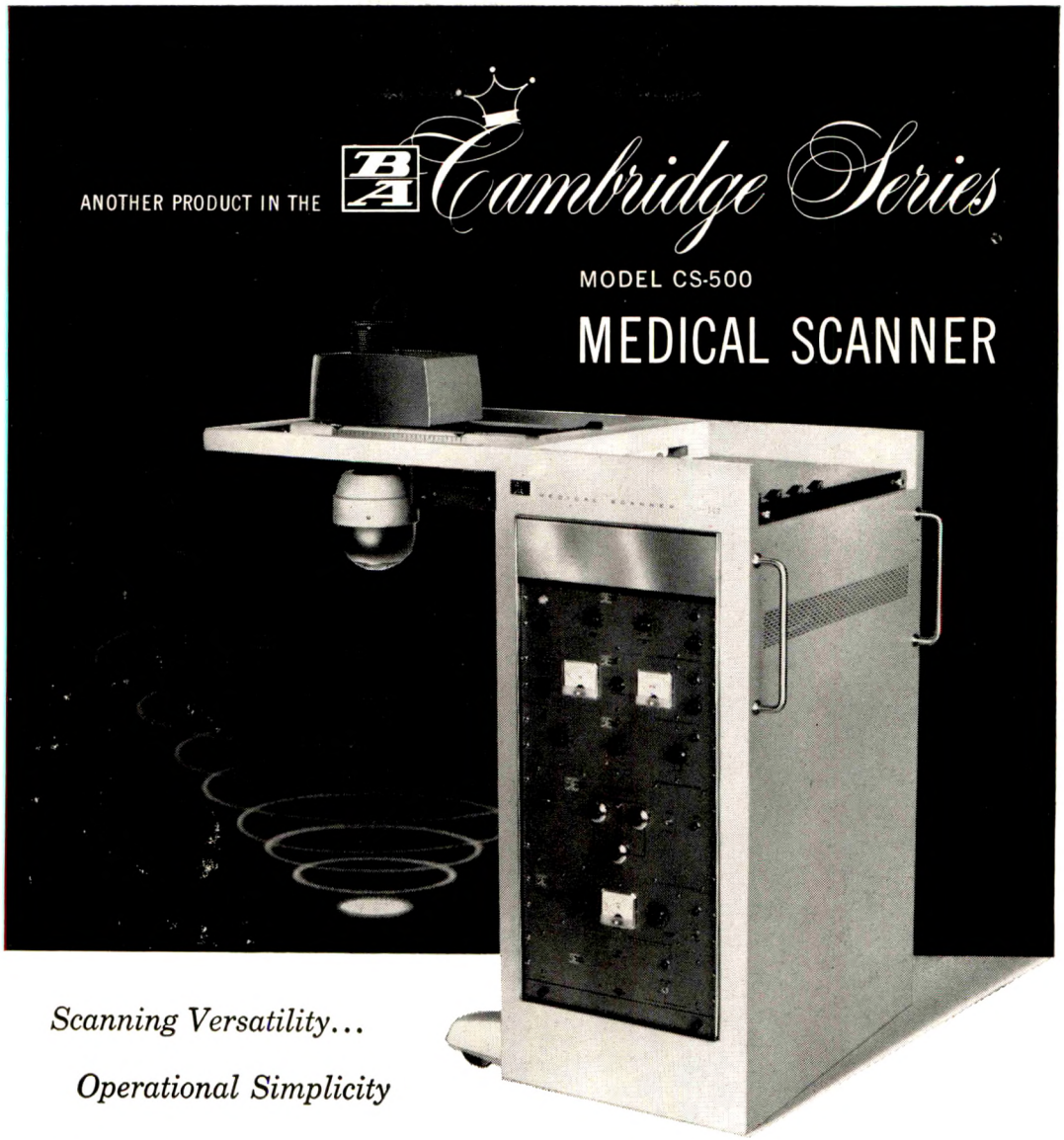
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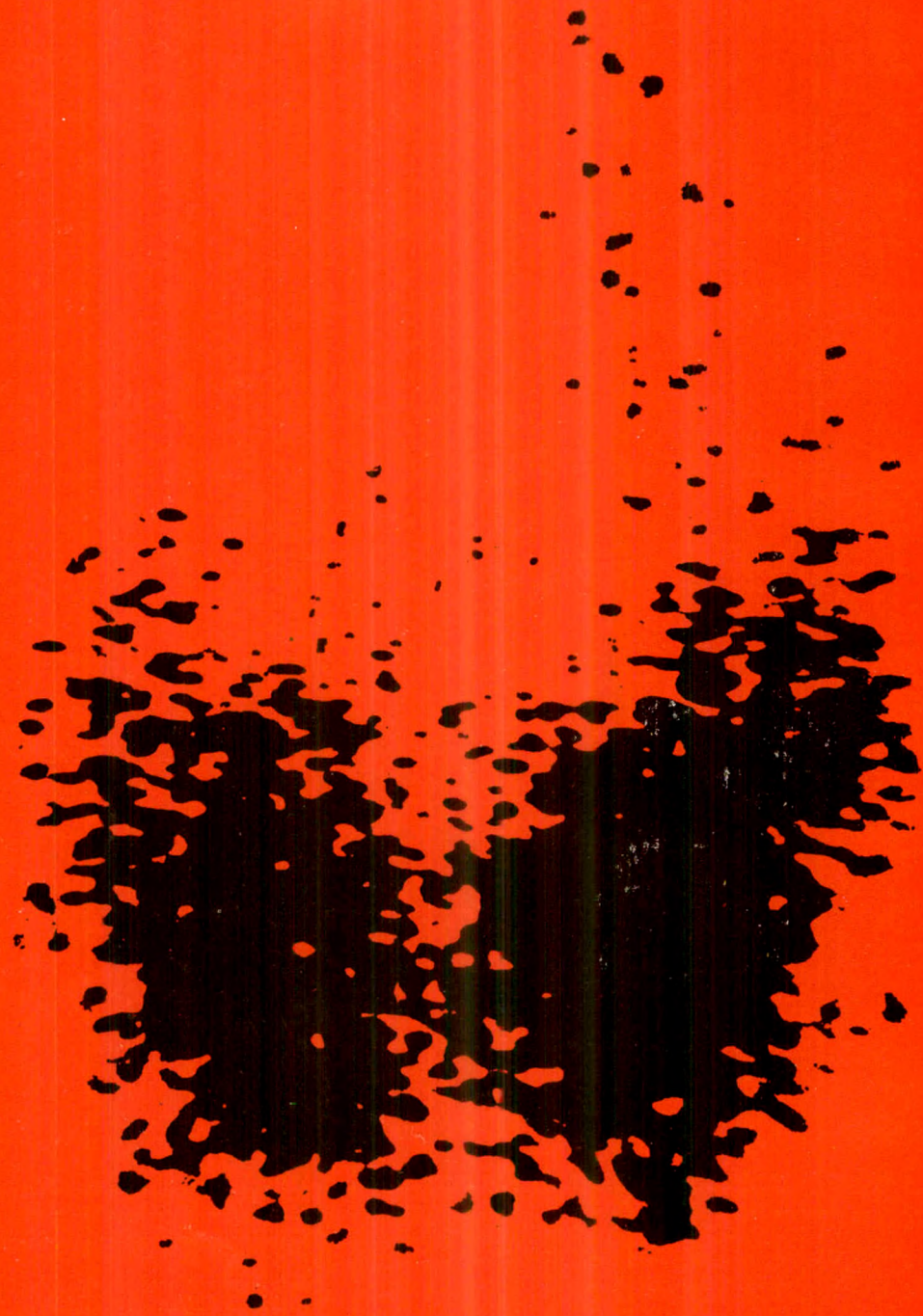
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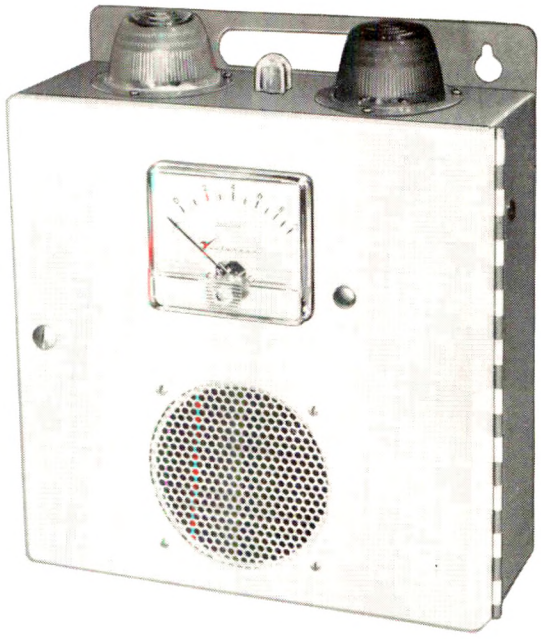
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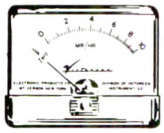
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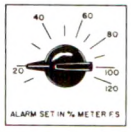
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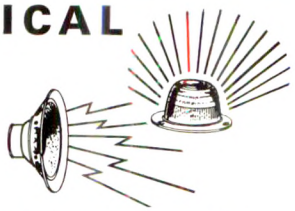
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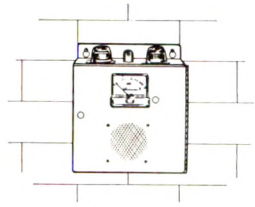
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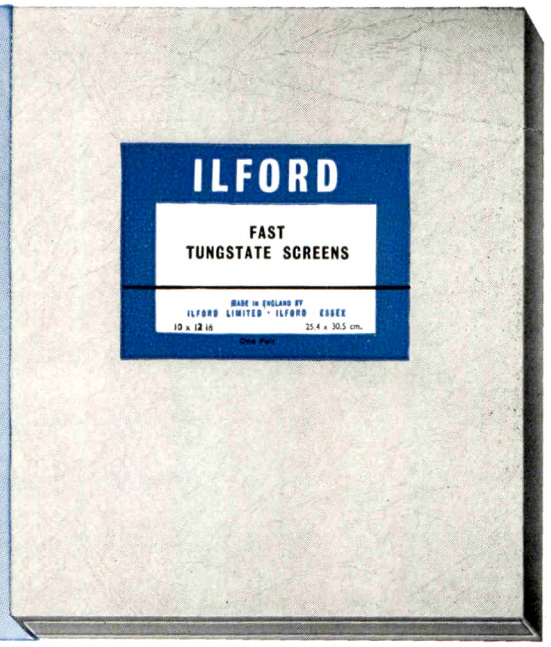
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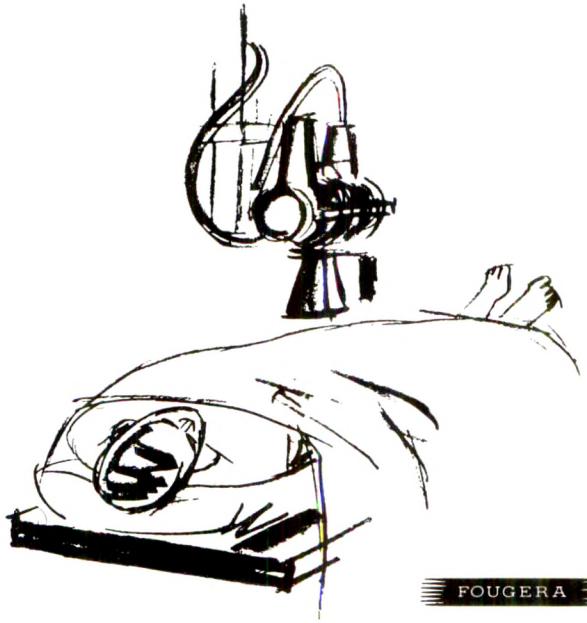
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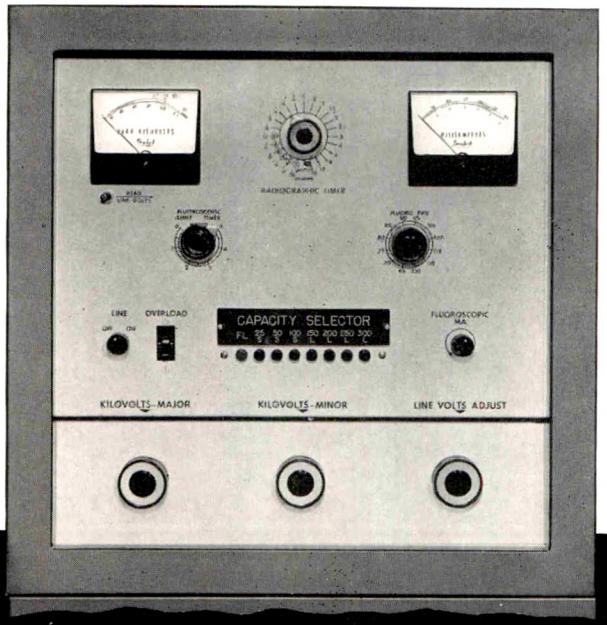
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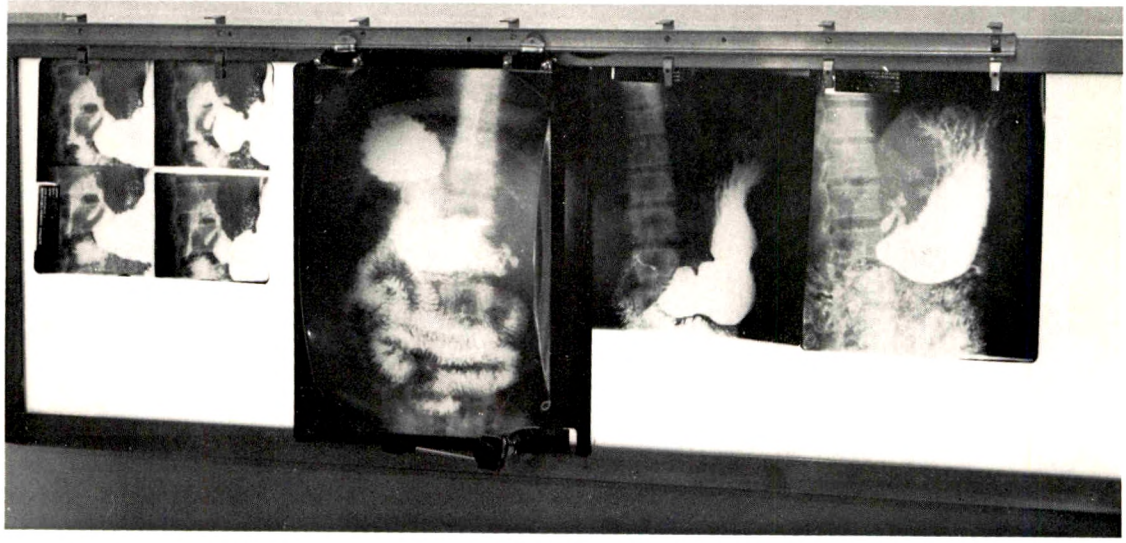
by J. R. Helff, M.D.
Radiologist, Middlesex General Hospital
New Brunswick, New Jersey

Back when a ten-inch TV screen was a luxury, thousands of magnifiers were sold—large lenses, shaped of LUCITE® and filled with mineral oil—that now gather dust in attics and junk shops across the country. But these lenses can still be valuable to the radiologist who wants to view a 14 x 17 film with full magnification. And the lens arrangement shown here (see photo) has the advantage of simplicity, economy and convenience.

The lens slides laterally on hanging-door hardware: an aluminum track and nylon rollers that take the weight easily and give smooth movement. Nylon rollers on the bottom of the magnifier make it slide easier and also keep the lens in parallel plane with the films. And a small knob on the magnifier lets you move it without getting fingerprints on the lens. The aluminum track extends 18 inches to the left of the view box so the lens can be "parked" out of the way.

Different degrees of magnification result when the distance between the LUCITE lens and the film is varied. On this unit the lens is mounted about 1½ inches from the film on view box. The distance could be increased up to six inches without distorting the images. With this mechanical arrangement it is easy to change films, to view films in sequence or to slide the lens entirely out of the way.

The cost of creating your own magnifier will vary, but shouldn't be more than ten or fifteen dollars. This lens cost $1.00 in a junk shop. (Don't be discouraged by light scratches on the surface of a used magnifier—these can be polished away with a plastic rouge.) The hanging-door hardware was $6.00. And the handle on the magnifier came from a discarded camera tripod. Put these elements together and you've got a permanent, excellent piece of equipment that can't be found commercially—and that would cost you much more if it could.



OVER

SIMPLIFIED TUNNEL VIEW OF THE KNEE

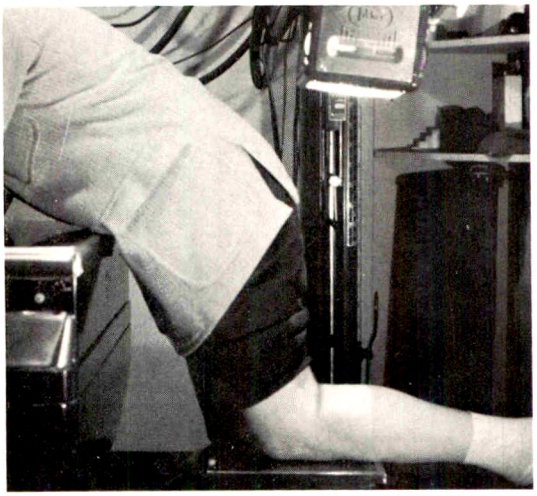
by G. L. Flitcroft, R.T.—Mercy Hospital, Watertown, N. Y.
Verna Faye Summers, R.T.—Drs. Sickels, Cosgrove, McCreary, Watertown, N. Y.

For this tunnel view of the knee (see radiograph A) place the patient at the end of the x-ray table, standing with his weight supported by the table.

The knee to be radiographed is placed on an adjustable stool, set at a comfortable height. Put an 8 x 10 cassette under the knee and position the femur at 10° off the vertical (see photo B). The tube is tilted 5° cephalad, so that the central beam will pass through the knee at a point about ½ inch above the joint space.

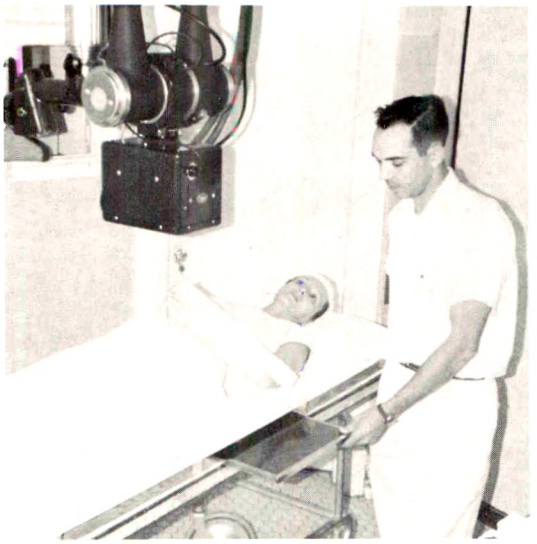
For a starting technique, on an average patient, try this: 100 MA for 1/10th of a second at 70 KvP, with a 40 inch distance.

(B) Photo by T. N. Sickels, M.D.



(A) Radiograph





X-RAY TUNNEL CART

by Don L. Blancett, Chief X-ray Technician
St. Joseph's Hospital
Kansas City, Missouri

We designed this tunnel cart (see photo above) to reduce the number of times a seriously injured patient has to be moved. The patient is placed from the ambulance cart onto the tunnel cart and taken into the x-ray examination room. Grid cassettes or regular cassettes with a wafer grid are used to make the x-rays. Then the patient is left on the cart and moved to the next destination.

Patients for recheck hips can be taken into the x-ray examination room on the cart, x-rayed and left on the cart until the films are checked. This cuts examination time 75% by leaving the room open for the next examination, while the first set of films is developed and inspected.

The tunnel cart also works as an auxiliary x-ray table when schedules are heavy. It is particularly convenient for examination of the shoulders, the abdomen, or for the two-hour stomach check.

You can make your own tunnel table without great expense. Use half-inch plywood for the bottom of the "tunnel," ⅜-inch plywood for the top. One-inch dowels, cut about two inches long, are spaced about 18 inches apart to separate the two layers of plywood. One caution: before construction, make a few x-rays of your top layer of plywood to be sure there are no radio-opaque spots in it.

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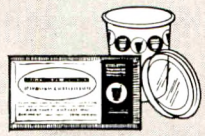
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MODERN RADIOLOGY IN HISTORICAL PERSPECTIVE *by* **Stephen D. Dewing,** *New York Univ.* Previous articles and books have all dealt with specific, limited aspects of the subject. Now for the first time all available material has been pulled into a *unified, balanced picture.* The author has covered radiology from its beginnings including all branches—**medical, nonmedical,** and **nuclear.** The careers of the founders of radiology are reviewed in detail . . . Röntgen, Becquerel, and the Curies. Other sections cover the development of physics, radiographic apparatus, radiologic periodicals and organizations since 1895, radiation hazard and protection, and finally, the present day status of clinical radiology. *Aug. '62, 200 pp., $5.75*

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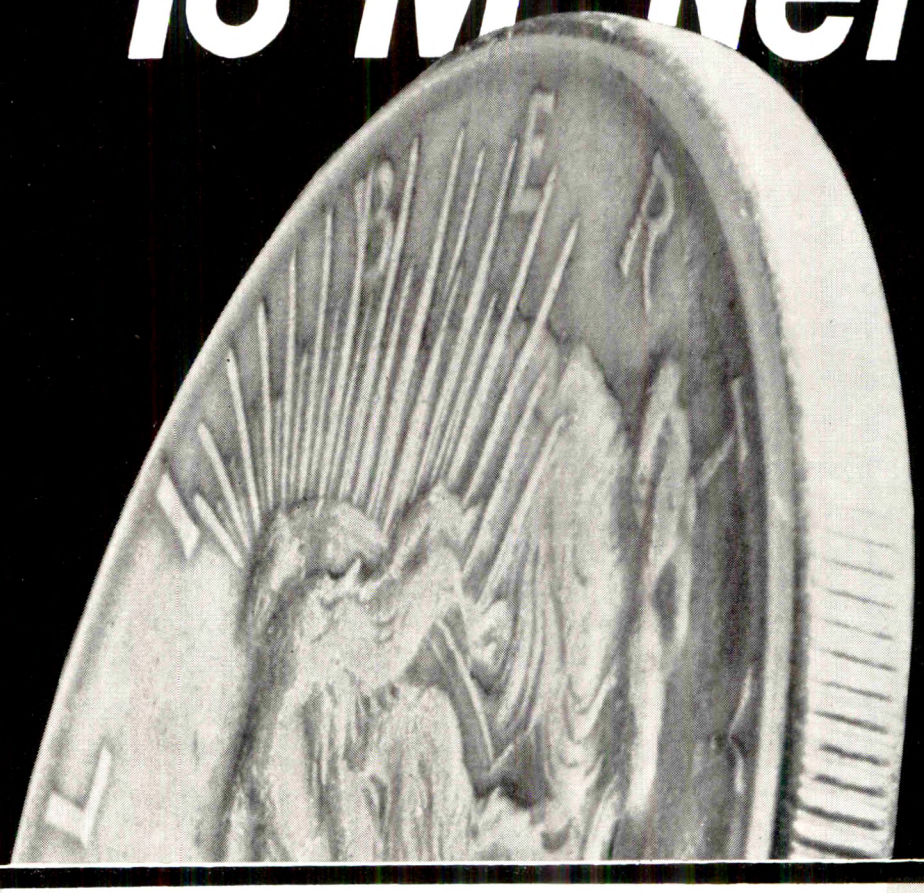
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ROBERT L. BROWN, M.D.

THE AMERICAN JOURNAL OF ROENTGENOLOGY
RADIUM THERAPY AND NUCLEAR MEDICINE

VOL. 89 JANUARY, 1963 NO. 1

THE OBJECTIVES OF THE AMERICAN RADIUM SOCIETY*

THE PRESIDENT'S ADDRESS

By ROBERT L. BROWN, M.D.
ATLANTA, GEORGIA

THE American Radium Society was formally organized on October 26, 1916, 46 years ago, at the Rittenhouse Hotel in Philadelphia, Pennsylvania. There were 19 active members and 1 associate member at the first meeting. The founding group included 10 surgeons, 5 radiologists, 3 dermatologists, 1 internist and 1 physicist. The first President was W. H. B. Aikins, a Canadian internist who had become interested in radium. Thus, from the very beginning the American Radium Society has included in its membership representatives from various specialties drawn together by a common interest. Also from the beginning it has been international. Our present active membership in the United States, Canada and Puerto Rico includes 113 therapeutic radiologists, 112 general radiologists, 85 surgeons including 27 gynecologists, 18 physicists and 30 physicians engaged in other specialties such as dermatology, pathology, pediatrics and internal medicine. The United States, Canada, England, Scotland, France, Sweden, Denmark, Switzerland, India, Mexico, Puerto Rico, Cuba, El Salvador, Guatemala, Venezuela, Argentina, Colombia, Peru, Brazil, Chile, and Uruguay are all represented in our active or honorary membership.

Throughout its life the American Radium Society has been a meeting ground for those whose interests have as a common denominator the study of malignant disease and the agents most effective in its treatment with particular attention to radium, x-ray and other sources of ionizing radiations. This is not a radiological society, not a surgical society, but an interspecialty organization. Furthermore, it has remained small enough so that many of the members know each other personally and welcome the annual meetings not only for the scientific programs but for the opportunities which they present for exchange of ideas informally between individuals or in small groups. All in all it seems to me, and I hope to you, to be a most worthy Society.

There have been only two changes in the

* Presented at the Forty-fourth Annual Meeting of the American Radium Society, New York City, April 2–4, 1962.

statement of the objectives of the American Radium Society since the original constitution was drawn up. In the beginning the objective of the American Radium Society was expressed in this way: "The object of the Society is to promote the scientific study of radium in relation to its physical properties and its therapeutic application." This seemed adequate for many years but x-ray assumed ever greater importance in radiation therapy, and discoveries in the field of atomic physics made new sources of ionizing radiation available for medical use. A new expression of purpose was needed and the members of the American Radium Society decided to change the objective as stated in the constitution so that these developments might be included. Accordingly, in 1950 the paragraph in our constitution describing objectives of the Society was reworded to read as follows: "The objective of the Society shall be to promote the scientific study of radium and other sources of ionizing radiation in relation to their physical properties and their therapeutic application."

Ever since it was founded, this Society has encouraged liaison between members of various specialties interested in combating cancer, one of mankind's deadliest enemies. For any group of physicians and scientists interested in cancer, it was a reasonable and natural development that consideration should be given in our scientific programs not only to the study of the effect of ionizing radiation on malignant tissue and the value of this agent in the treatment of cancer but also to an evaluation of it when compared with other therapeutic methods. Furthermore, our members became interested in combinations of radiation and surgery in a constant search for the best method to aid the patient who has cancer. More recently, with the development of cancer chemotherapy there has been an increasing interest in chemical agents particularly as they may affect the response to irradiation. Although the biologic effect of radiation had been investigated by members of this Society, it had not been mentioned formally and it seemed wise to include the study of the biologic effects of radiation in the statement of objectives recorded in our constitution. Thus, the American Radium Society has become concerned with the physical properties, biologic effects and therapeutic application of radium, x-rays and new sources of radiation made available through atomic research, with physical and chemical agents modifying radiation response, with the interrelationship of radiation and surgery and to a limited degree at least with the whole cancer problem. Only those surgeons, pathologists, dermatologists, pediatricians, and internists who are deeply interested in this problem and who are giving a significant portion of their time to the study and treatment of cancer qualify for membership in the American Radium Society, and the radiologists who are members of this organization belong because of their interest in radiation as it is related to the treatment of cancer. Because of these facts, it seemed appropriate a year ago to make yet another change in the statement of objectives as recorded in our constitution and this paragraph now reads: "The objectives of the Society shall be to promote the scientific study of radium and other sources of ionizing radiation in relation to their physical properties, their biologic effects, and their therapeutic application; and to encourage liaison between the various specialties concerned with the treatment of cancer."

This is in no way intended to change the character or composition of our Society. It simply recognizes something that has been present since the very beginning and puts into words what has been expressed by our actions over the years. We have encouraged liaison between the various specialties interested in cancer and allied diseases and it is our opportunity as well as our responsibility to continue to do so. This is an age of superspecialization and the names of scientific societies reflect this as, for instance, the Society of Head and Neck Surgeons, the Society of Pelvic Surgeons, the Society for the Study of Nuclear Medicine and, of

course, the larger organizations such as the American Roentgen Ray Society, the Radiological Society of North America, the American College of Radiology, the American College of Surgeons and many others. These are all directed toward worthwhile ends and serve useful purposes, but their memberships are not as broad as ours and they do not afford the opportunity for radiologists, surgeons, physicists, internists, and other specialists to sit down together and give earnest consideration to one of the most challenging medical problems of our time. Although the future of cancer therapy may belong to the biochemist and the immunologist, surgery and irradiation are the most effective agents now at our disposal for the treatment of cancer. Radiologists need to know what surgery can do and surgeons need to know what radiation can do, and they need to explore more completely the possibilities of combined therapy. Sometimes the cancer patient is treated by radiation because he happens to see a radiologist first or by surgery because he happens to see a surgeon first. We must not compete for the care of the cancer patient but work ever more closely together so that the decision regarding therapy rests securely on what is best for the patient. Only through a better understanding of what all modalities can offer will it be possible for us to make this decision correctly.

This is essentially a plea for cooperation. We have a fine heritage. Our members are leaders in the cancer field. Our opportunity in the future is unlimited. It seems to me that we have the best and most comprehensive approach. Let us make the most of it and work together toward the day when we can speak not of the problem of cancer but of its conquest.

Robert Winship Clinic
Emory University
Atlanta 22, Georgia

CLINICAL TRIALS IN THE NEXT DECADE*

By JOHN R. HELLER, M.D.†
NEW YORK, NEW YORK

THE role of radiation in the treatment of neoplastic diseases should be increasingly important in the next decade. This seems a rational forecast in light of the background of this phenomenon which has demonstrated an ability to alter the reproductive integrity of the cell. Moreover, without indicting the scope or value of surgery, one can be persuaded to the opinion that the cancer surgeon might be approaching his zenith. The boundaries of surgery are probably limited only by the ingenuity of the operator, aided as he is by vast supportive techniques which enable the organism to withstand the rigors of surgical extirpation. Nevertheless, there are boundaries, short of total control of malignant growth, which surgery cannot exceed. These exist in widely disseminated cancers, the leukemias and the lymphomas. It is in these areas that we usually think of other modalities, including radiation, as being the most likely to develop means of control.

Whether or not radiation has demonstrated its finest potential is academic when it is recognized that surgery, because of practical values, has been, and still is, in the vast majority of early and moderately advanced cases of malignancy, the treatment of choice.

Radiation obviously has been the stepchild in many instances and has not been called upon to demonstrate its own peculiar merits to any marked extent in destroying the neoplastic cell.

If this is so, in the future radiation may well be given an opportunity to develop its fullest resources. This means that radiation treatment will receive a much more extensive critical review than heretofore as a first step in more practical development as a clinical tool.

To do this calls for accurate utilization of the device known as "Clinical Trials," and it behooves any of us working in this area to become familiar with some of the criteria necessary for the accurate use of this investigative method. Sometimes we overlook the elementary steps which are essential to experimental trials if our results are to be accepted as conclusive. Briefly, we might look at some of these criteria.

I. DEFINITION OF POPULATION

Before one undertakes clinical trials involving the use of ionizing radiation, or any other modality for that matter, it is necessary to strictly define the type or types of patients to be treated. For instance, the definition might simply be "all patients treated at a particular center, or from a particular area," or "patients selected for radiation treatment from all those available at a particular center," and in this case the reasons for selection should be closely defined, such as, inoperable, a specific type of cancer, or any other reasons of selectivity having some bearing on the method being tested. Such factors as stage of disease, age limitation, or even socio-economic conditions may have to be considered in defining the population to be treated.

The reasons, of course, for such definition are obvious although they are sometimes overlooked. Failing to use care in defining the type of patient to be treated leads the investigator to inadvertent selection of his results. He may well find in the end that his conclusions are colored by artifacts which have entered into his study.

* Presented at the Forty-fourth Annual Meeting of the American Radium Society, New York City, April 2–4, 1962.
† President, Memorial Sloan-Kettering Cancer Center, New York, New York.

Hence, the results are not only impossible of accurate interpretation but may even be misleading.

2. RANDOM ASSIGNMENT AND CONTROLS

Once the population has been carefully defined, it is necessary to establish controls which will provide a basis for accurate and meaningful comparison. Naturally, these groups must be matched and patients randomly distributed so that statistical values will have some significance. One of the pitfalls in this area occurs when a matching population is selected as controls presumably under similar conditions and approximately parallel with all other criteria except for the dimension of time. In such a case, errors are almost certain to result. A classic case can be cited from experience at the Radiumhemmet. It has been pointed out that, without any marked change in the philosophy of treatment at that institution during the thirties, a definite improvement was seen for each 5 year period. Yet, this is explained as resulting simply from a better understanding of the application of the principles of treatment during each 5 year period. Comparing one group with another, unless they are contemporary, may well lead to erroneous conclusions.

3. CRITERIA OF EVALUATION

Failing to define criteria for evaluation of results would be much like playing baseball without any rules. A home run and a single might have the same weight, depending upon the mood of the umpire or the viewer. As to who won the game would depend entirely on personal bias. Hence, in clinical trials we must have ground rules established well in *advance* of our research to guide our conclusions as to what we are finding. The relative benefits of the various treatments tested will have significance only if the criteria by which we measure them are understandable and clearly defined prior to our study. Such criterion as longevity may be one of our important benchmarks by which we can evaluate results. If so, such a finding must be provided for and adhered to as the important criterion for evaluation. Recurrence of disease may also be part of the plan for conclusive findings and the time at which recurrence occurs will be a factor. The appearance of metastasis or the spread of primary tumors may be used to evaluate results, but if so, they should be so defined. Agreement on criteria is vital to objective results.

4. FOLLOW-UP PROCEDURES

The importance of following all patients within a study group cannot be overemphasized, and uniformity of the quality of care for patients during follow-up is most essential. In most studies it is frequently necessary to establish a unit to be responsible for the care of all patients participating in a clinical trial so that conditions of treatment and care can be strictly controlled. Without these conditions a variable can easily occur. Individual patients or a group of patients within a study population who received more or less care than the standard would undoubtedly produce a variable which, even if detected, would color the final results.

5. SIZE OF POPULATION STUDIED

The numbers of patients to be studied will have a direct bearing on what we are attempting to learn. The number of patients must be determined by the degree of difference expected or acceptable. In general, the degree of difference should be inversely proportional to the number of subjects studied. If a small difference is anticipated, one must plan on a large number of patients. A smaller study population can be used if a large numerical difference results. Usually, however, such a probability is not typical of clinical trials. Also related to the size of a study population is the significance of the percentage of results obtained. Although even in a large number of patients a small percentage might be statistically significant, it would have little

practical meaning. It should be accepted that in determining the number of patients one must first decide what degree of difference is acceptable as "no difference." Then beyond this, what percentage of results will have real meaning in relationship to the problem of demonstrating a possible improvement in the treatment of cancer, if this is our goal.

In stressing the importance of clinical trials in relation to ionizing radiation, it should be emphasized that the radiotherapist must utilize this method of study to demonstrate both the usefulness of standard techniques and the merit of newer ones now emerging. One of the areas which may be most rewarding might resolve the question as to preferred treatment for certain cancers; for instance, in treating head and neck cancers, there seems to be room for question as to whether surgery or radiation will yield the best results. Design of a clinical trial, with proper regard for criteria such as population definition, random assignment, controls, follow-up procedures, etc., could establish some authoritative data for guiding the clinician in choosing the therapy most suitable for the patient.

Also to be explored by means of clinical trials are many questions as to the value of palliative treatment in cases of widely disseminated cancer. Heretofore, data have been presented on results of irradiation of various metastatic lesions, but a clear picture of results, because acceptable follow-up procedures were lacking, is seldom obtained. Clinical trials which could assess results in comparison to other modalities are necessary before palliative radiation for many sites of cancer can be demonstrated.

A much greater challenge faces radiation in the rising promise of its use in combination with other modalities, surgery and chemotherapy. As this work proceeds, it will be necessary to measure its effect on cancer mortality, or its relative merits in relation to irradiation alone or to the other treatment methods. Radiation as an adjunct to surgery will undoubtedly prove valuable in treating certain neoplasms, but again only carefully managed clinical trials will demonstrate this satisfactorily.

We are already witnessing some of the possibilities of chemicals as potentiators and sensitizers in combination with radiation therapy. Preliminary results have been obtained by some investigators with alkylating agents, particularly in treating lung cancer. So far, the data on improving survival have not proved significant, although there is good evidence that extensive tumor regression was obtained. Also a number of studies have shown that localized lymphoma responds better to roentgen ray and nitrogen mustard therapy than to irradiation alone.

The value of antibiotic chemotherapy may prove to be most useful only in combination with radiation. Actinomycin D, which has not been impressive when administered alone, has shown considerable promise when used sequentially with radiotherapy. Some solid evidence with well controlled clinical trials is now needed in this area, as it appears that this substance has a definite enhancing effect on radiation.

Attempts to improve the action of radiant energy in altering the reproductive integrity of the neoplastic cell have included, aside from chemical stimulators, studies involving oxygen tension. Dr. L. H. Gray,[3] the British radiobiologist, after reviewing the literature suggests that oxygen tension is a factor in the effectiveness of irradiation. He points out that the association between dose and cure rate may be due to the degree of anoxia existing in different tissues. It has been shown that cells are on the order of from two to two and one-half times more radiosensitive with normal oxygen tension than cells in anoxia. Other studies indicate that something on the order of twice the dosage of radiation is required on hypoxic cells to produce the same response as on aerobic cells.

During the past few years, radiobiology has made much progress, and the knowledge of how radiation affects the mitotic process will lead to new discoveries that

can have a profound effect on the use of this modality in controlling neoplastic diseases.

As Kaplan[4] points out, the irradiated cell is the site of a series of chemical reactions, ranging from free-radical formation to bond rupture which may result in profound biologic consequences. There are several factors which mediate demonstrable changes in the cell, including absorbed dose, mitotic activity and the length of time available for repair processes. Much of the present biochemical studies are focused on learning more of the genetic death of the cell which, in effect, is the result of ionizing radiation. Other processes may continue with apparent little change and even mitosis may proceed partially or even completely for several cycles before responding to the subtle alterations which have been wrought.

It seems necessary that those attempting to demonstrate the role of irradiation in treatment of neoplasms should be abreast of current research efforts into the fundamental effects of this potent force.

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CONTRAST EXAMINATION OF THE LARYNX AND PHARYNX

GLOTTIC, INFRAGLOTTIC AND TRANSGLOTTIC TUMORS

By SUMNER HOLTZ, M.D.,* WILLIAM E. POWERS, M.D.,* MALCOLM H. McGAVRAN, M.D.,† *and* JOSEPH OGURA, M.D.‡
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IN PREVIOUS publications we have described the technique of contrast examination of the larynx and pharynx, the accuracy of this diagnostic procedure, and its value in the treatment of cancer.[4,5] The differentiation of transglottic and infraglottic tumors from pure glottic lesions is vital when one considers the difference in prognosis and therapy.[1] In the assessment of extent and size of laryngeal tumors, a comparison between the clinical methods of indirect and direct laryngoscopy and the roentgen contrast study has demonstrated the superiority of the latter method.[4] The roentgen features and criteria for the assessment of the site and extent of the tumor become, then, a most important step in the management of these cases. These criteria predominantly involve gross anatomic changes which are readily apparent.[2,4,5] Since the examination is a physiologic study, changes of function also can be evaluated.

Our experience with cineroentgenographic studies has not enhanced our diagnostic ability, but to the contrary has proven that any functional impairment is readily demonstrated on the "still" technique.[3]

NORMAL ROENTGEN ANATOMY

The normal roentgen anatomy and function of the larynx in its relation to the various maneuvers have been previously described.[5] However, a brief review of the anatomy of the glottic and infraglottic portions of the larynx seems in order.

1. *Vocal Cords.* The vocal cords are paired horizontally-placed folds that run from the vocal process of the arytenoid to the angle between the two lamina of the thyroid cartilage. They do not meet in midline anteriorly but rather at this point are adjacent to one another. Between them anteriorly is the anterior commissure. Since they are attached posteriorly to the vocal process of the arytenoid, they do not extend the full anteroposterior dimensions of the airway. They are normally smooth in outline, and for practical purposes, symmetrical. During respiration and phonation the vocal cords do not lie in a horizontal plane, but rather slope gently upwards from anterior to posterior. Because of this, frontal roentgenograms distort their thickness.

2. *False Cords.* The ventricular folds (false cords) are paired folds that lie just above and slightly lateral to the vocal cords. They extend from the anterolateral aspect of the arytenoid to the thyroid cartilage. Like the vocal cords they do not join in midline anteriorly and are present only in the anterior two-thirds of the sagittal plane of the larynx. They are of similar size to the true cords and are smooth and nearly symmetrical.

3. *Ventricle.* The ventricle (sinus Morgagni) is a cul-de-sac of varying depth that runs between the true and false cords. It extends upward from the upper and lateral margins of the true cord in such a manner that the false cord forms not only its "roof," but in part, the medial wall. Since it follows the cords, it extends anteriorly but not all the way to midline. The plane of the ventricle, like the cords, is ordinarily not horizontal but rather slopes gently upward and backward so that some distortion oc-

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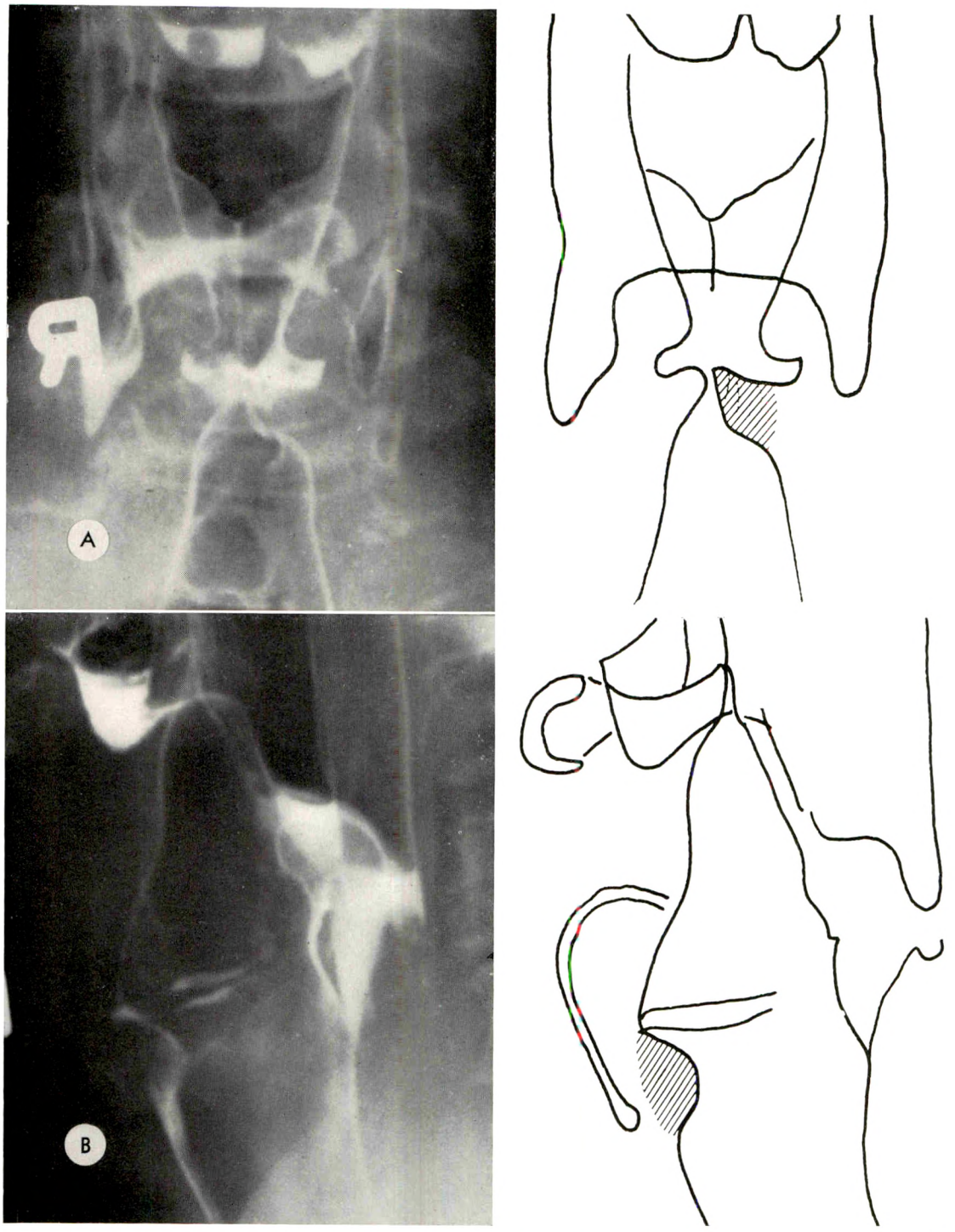


Fig. 1. Carcinoma of the left true cord with involvement of the anterior commissure. (*A*) Frontal view. The left true cord is enlarged and distorted. The ventricle is normal and the infraglottic space retains its normal appearance. (*B*) Lateral view. At the level of the true cord there is separation of the contrast substance from its normal relationship to the thyroid cartilage. This was a constant finding. Since the cord does not anatomically exist at this piont, the anterior commissure must be involved. At surgery a tumor was found involving the left true cord and anterior commissure.

curs on the frontal roentgenograms. It is smooth in outline, smallest in height medially and largest laterally.

4. *Infraglottic Space.* The infraglottic (subglottic) space is that area of the larynx extending from the inferior margin of the true cords to the second tracheal ring. During phonation and Valsalva maneuvers this portion of the larynx is delineated by a sharp right angle at the bottom of the true cords. The walls anteriorly, posteriorly and laterally are smooth in outline.

5. *The Base of the Epiglottis, Anterior Commissure and Infraglottic Space.* This aspect deserves special mention for it is at this site that small tumors can extend and hardly be detected by roentgenography. This is a critical area in the classification and hence in the treatment of laryngeal tumors. Because neither the cords nor the ventricle extends to the exact midline, the base of the epiglottis, the anterior aspect of the rima glottis and the anterior aspect of the infraglottic space are a continuous surface. This is demonstrated on the roentgenograms by a smooth contrast outline that is separated from the thyroid cartilage by only a few millimeters. Occasionally, at the level of the ventricle, this line becomes stepped backwards slightly for a millimeter or so—this being due to the thyroarytenoid muscle which may be inserted into the thyroid cartilage medial to the vocal cords.

6. *Arytenoids.* The arytenoids occupy the posterior third of the larynx and together with the mass of the corniculate and cuneiform tubercles are identified on the laryngograms. They are best seen at the time of the modified Valsalva maneuver as paired masses lying posteriorly above the plane of the cords. When the hypopharynx is not overly filled with contrast substance, movement of these structures can be demonstrated. Between the paired arytenoids is the interarytenoid notch which is a specific landmark for these structures. The arytenoids are smooth in outline, but are prone to edema and distortion even though they themselves are not involved by any pathologic process.

ROENTGEN FEATURES OF TUMORS

A. GLOTTIC TUMORS

1. *Limited to the True Cord.*

a. Enlargement (Fig. 1, *A–C*; and 2, *A–C*). Often, when the tumor is limited to the true cord, the only roentgen feature is an enlarged cord. This is especially noticeable when compared with the other side. It may also be distinct because of an asymmetrical ventricle, the one on the involved side being encroached upon by the enlarged cord. The surface of the cord may be smooth or irregular. Enlargement *per se* is not direct evidence that there is cancer present, as it may occur with a variety of benign processes (hyperkeratosis, vocal nodule and tuberculosis) (Fig. 3). As in other locations, laryngoscopy and biopsy are necessary associates of this procedure.

b. Polypoid mass (Fig. 4, *A* and *B*). At times a tumor is exophytic presenting as a polypoid mass. It may attain a size large

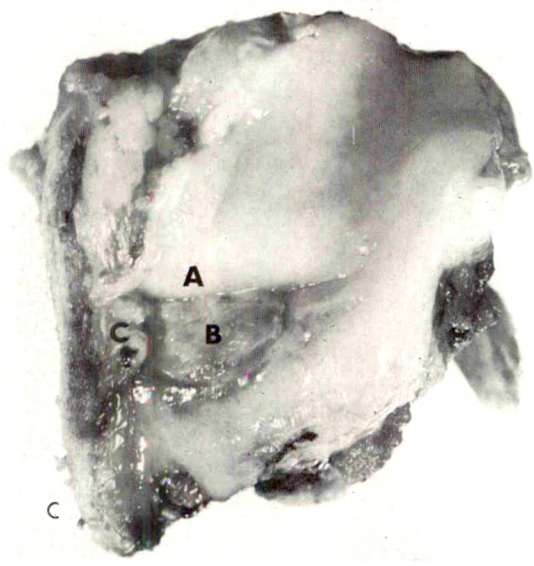


FIG. 1. (*C*) Hemilaryngectomy specimen shows tumor involving the anterior two-thirds of the true cord (B) with involvement of the anterior commissure (C). The tumor extends to the margin of excision. The false cord (A) is uninvolved.

RADIOTHERAPY IN THE TREATMENT OF PRIMARY OPERABLE CARCINOMA OF THE BREAST WITH PROVED LYMPH NODE METASTASES*

APPROACH AND RESULTS

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A LARGE number of patients with carcinoma of the breast is seen every year in a department of radiotherapy, especially in a cancer hospital. This patient material includes representatives of every phase and stage of the disease, with the exception of patients with very early carcinomas, and can be divided into the following groups: patients who are referred for postoperative radiotherapy; patients who are treated for recurrent or metastatic disease; patients with advanced inoperable carcinomas who are inoperable according to the original clinical classification by Haagensen and Stout (Table I).

During the last years, a new and unusual category of patients has been added at the Francis Delafield Hospital in New York to these previously mentioned groups. This is a group of patients, who clinically could be classified as operable in accordance with the clinical criteria set up by Haagensen and Stout, but who are now classified by Haagensen as inoperable because biopsies of the highest axillary lymph nodes and/or internal mammary lymph nodes showed disease before the mode of treatment was decided upon. These biopsies are now taken routinely in every patient who is referred to the Francis Delafield Hospital. The indications are shown in Table II. This table also shows that we are now taking double biopsies in patients whose disease is clinically not too advanced and triple biopsies only in such patients who present themselves with clinically advanced lesions. This is a modification of an earlier approach, where triple biopsies were taken in most of the patients. As a result of this policy, approximately 50 per cent of the patients with primary, and apparently operable, carcinoma of the breast, who are referred to the Francis Delafield Hospital, are declared unsuitable for surgery because in Haagensen's opinion no surgical procedure, neither a radical mastectomy nor a superradical approach, can possibly remove all the disease when these lymph nodes are found to be positive. These patients are therefore treated with radiotherapy and a follow-up report of this material is pre-

TABLE I

CLINICAL CRITERIA OF OPERABILITY ACCORDING TO HAAGENSEN AND STOUT

Carcinoma of the breast is inoperable when:

1. Extensive edema of the skin over the breast is present
2. Satellite nodules are present in the skin over the breast
3. The carcinoma is of the inflammatory type
4. Parasternal tumor nodules are present
5. Proved supraclavicular metastases are present
6. There is edema of the arm
7. Distant metastases are demonstrated
8. Any two, or more, of the following grave signs of locally advanced carcinoma are present:
   a. Ulceration of the skin
   b. Edema of the skin of limited extent (less than one-third of the skin over the breast being involved)
   c. Solid fixation of the tumor to the chest wall
   d. Axillary lymph nodes measuring 2.5 cm., or more, in transverse diameter.
   e. Fixation of the axillary lymph nodes to the skin or the deep structures of the axilla

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breast somewhere other than at the site of the dominant mass; it can often solve the problem of diagnosis in multinodular breasts or in breasts which have been previously operated on. In a small group of cases presenting bizarre symptoms, the presence of a malignant lesion which is completely missed by inspection and palpation is often discovered by mammography. This situation not infrequently occurs in large fatty breasts. Occult cancers can be revealed by roentgenography and, finally, periodic examinations of women with no breast symptoms above thirty-five years of age can be an efficient case finding method, revealing small lesions (as small as 0.5 cm. in diameter), the majority of which have not yet metastasized. This has already been done in a survey project during the past five years at the Albert Einstein Medical Center in Philadelphia. If these findings can be confirmed by more extensive programming, improved mortality statistics for cancer of the breast could at last begin to appear and this might more than justify the effort and expense entailed with mammography.

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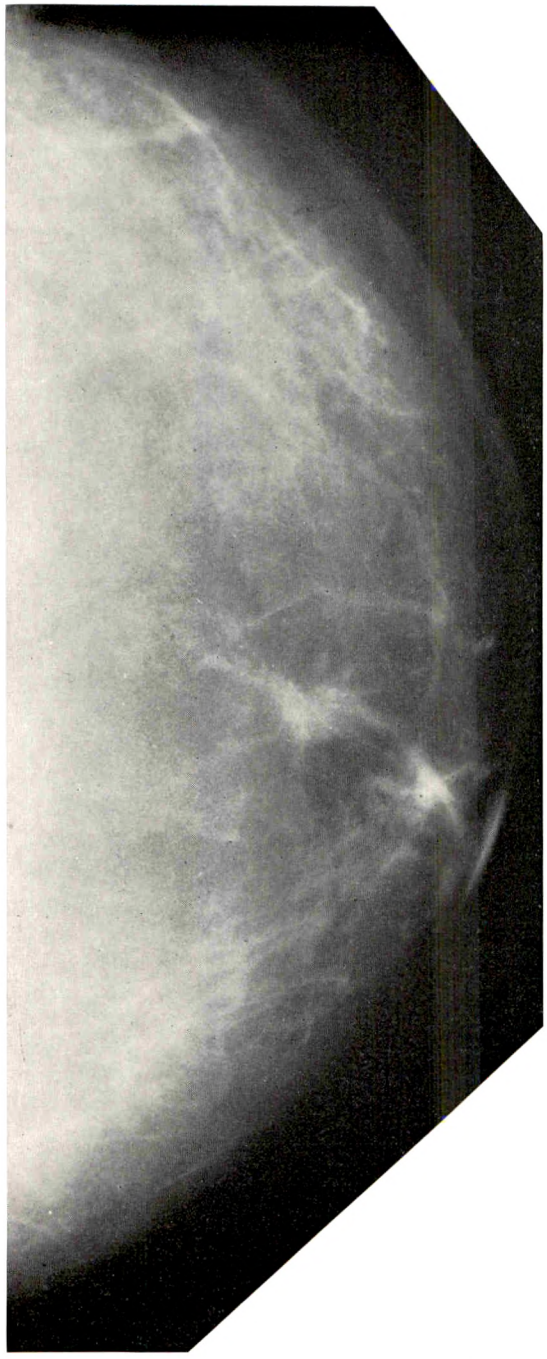


FIG. 7. As a member of the x-ray survey project, this asymptomatic, fifty-five year old woman was examined every six months. Both clinical and roentgen examinations were reported as negative from June, 1956 to June, 1960. Roentgenograms in June, 1960 revealed a small malignant lesion in the left breast and biopsy was strongly urged. The surgeon could palpate no masses in either breast and he was only persuaded to operate because of the roentgen findings. A tumor about 9 mm. in diameter was found corresponding to that seen on the roentgenogram. Radical resection was performed. The pathologist reported a duct carcinoma with no metastases to the axillary lymph nodes.

dependency is now taken for granted. Some races, such as the Japanese, have a low incidence, but it is not clear whether this is entirely a heredity trait or the result of prolonged multiple lactations.[8] Breast cancer patients tend to marry, become pregnant and nurse later in life than do non-cancer patients. They also tend to have fewer children and these are nursed for shorter intervals. Daughters and sisters of breast cancer patients have an increased risk of developing this disease.[19] Cancers of various growth potentials can appear in women of any age, but slow growing lesions are more apt to occur in the seventh and eighth decades.[17] A positive correlation seems to exist between breast cancer and endometrial cancer, but not with cervical cancer. Thus it seems that the endocrine system plays a vital role in the initiation and growth rate of breast cancer.[19]

The most common cause of death from cancer in women in most parts of the world is due to cancer of the breast. It is estimated that more than 60,000 women develop cancer of the breast every year in the United States alone. If mammography can materially help to reduce delay in diagnosis and treatment as suggested by our studies, and if among these 60,000 women, treatment of *localized* lesions could be increased by only 10 per cent, then the expense and effort entailed with mammography would seem more than justified!

SUMMARY

Roentgenography of the breast is a valuable adjunct in the clinical management of breast problems; it can serve effectively in avoiding delay when surgical interference is indicated; it can demonstrate whether or not a dominant mass is benign or malignant or whether there is a malignant lesion in the

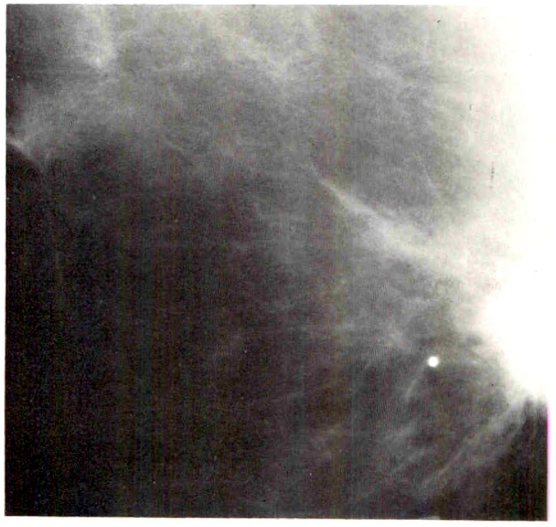


Fig. 5. The chief complaint of this fifty-one year old woman was a pus-like discharge from the right nipple for about eight months. A recent episode of redness and pain in the right breast led her to change to another physician who could palpate no masses, but suggested roentgen studies. An irregular spiculated mass believed to represent a carcinoma was reported by the roentgenologist and biopsy was urged. An intraductal carcinoma was found with no lymph node metastases.

this idea of "biological predeterminism."[10]

For practical purposes, breast cancers might be divided into three categories of growth rate: (1) very rapidly growing tumors; (2) moderate rapidly growing tumors; and (3) very slowly growing tumors.

In Group 1, we believe that early discovery and surgical intervention will have a minimum effect on mortality because these lesions grow rapidly and metastasize early and widely.

In Group 2 early diagnosis and therapy may have a very significant effect. If more lesions can be found which are still localized to the breast and so have not yet metastasized, then the five year cure statistics should be quite favorably influenced.[16,18]

In Group 3 prompt diagnosis and treatment would have some further beneficial effect beyond prevailing customs of management. These lesions grow slowly and metastasize late. They comprise a large portion of today's five year cures.

Unlike cancer of the skin, cervix and colon, cancer of the breast is influenced by many additional intrinsic factors. Heredity, size, structure and physiologic activity of the breast, aging, hormone balance, nutrition, trauma, bacterial and viral infections are factors to be appraised as in other diseases; but in breast cancer, two or more of these factors seem to be heuristically obligative so that the idea of hormone



Fig. 6. This sixty-two year old patient complained of occasional sticking pain in the lower inner quadrant of the right breast. Clinical examination revealed no dominant mass, but the patient asked for a roentgen examination to "relieve her mind." Roentgenograms revealed a scirrhous carcinoma in the lower inner quadrant of the right breast near the chest wall, confirmed by the pathologist. The axillary lymph nodes were free of metastases.

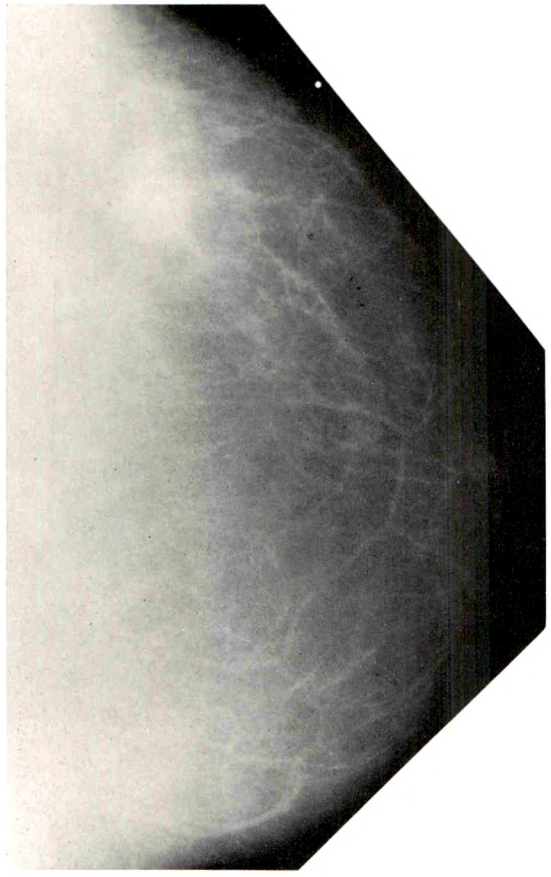


FIG. 3. This fifty-three year old patient was referred for roentgen studies by her physician who felt bilateral nodular masses, more numerous on the right. The patient was otherwise asymptomatic. A small poorly defined mass suggesting carcinoma was reported by the roentgenologist. Operation revealed the presence of a lesion reported as medullary carcinoma by the pathologist. No axillary lymph node involvement was found.

speculation based on voluminous retrospective analyses.

There is general agreement on some aspects of the complexities of breast cancer. For instance, it is widely recognized that much variation exists in the growth rate of different types of cancer. Grading of tumors, which was more popular years ago, is an attempt to apply prospective prognosis. In a sense, grading of tumors implies an awareness of different growth rates of cancers. But other factors besides the morphologic characteristics of the cancer cell determine growth rate. Here we agree with the concept of placing greater prognostic importance on the outcome of the "preclinical struggle for power between a developing neoplasm and the enigmatic defensive reactions of the host than on the time or type of treatment."[11] But we would prefer to comment in yet another way on

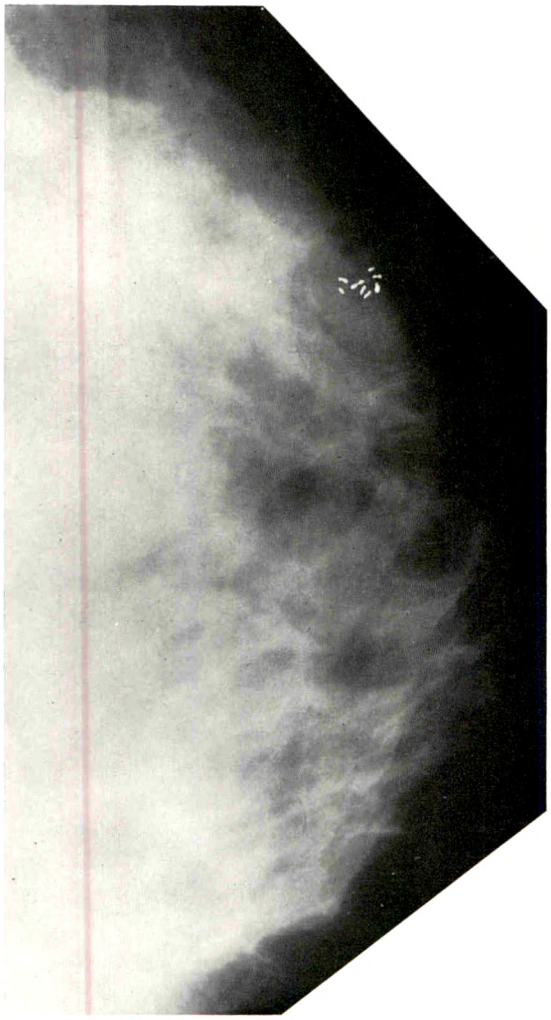


FIG. 4. This forty-one year old woman had a previous history of bilateral operations for benign lesions. She was admitted to the hospital for removal of a mass in the para-areolar area of the right breast, believed by the surgeon to be a cyst. A roentgenogram revealed a small area of calcific deposits (semidiagrammatic) suspected as evidence of malignancy by the roentgenologist. At operation, the lesion containing the calcium deposits was excised and on frozen section revealed a carcinoma. The other lesion corresponding to the palpable cyst was found to be a cyst.

The results of a recent x-ray survey project conducted at our institution further emphasized the potentialities of mammography.[2] Studies of 1,055 women over the age of thirty-five years were made semiannually for five years. No woman was admitted to the project if she had breast complaints. Cancer was found in 23 cases, the lesions averaged 1.1 cm. in diameter, and axillary metastasis was present in only 30 per cent, *i.e.*, 17 of these 23 cases were free of axillary metastasis. If the results of this pilot survey can be confirmed by more comprehensive programs, an improvement at last might be witnessed in the mortality figures for breast carcinoma.[4,6,7,15] In the meantime, the question will be raised: Will early detection and prompt surgical action have a beneficial impact on mortality rates?[14] This brings us into the realm of

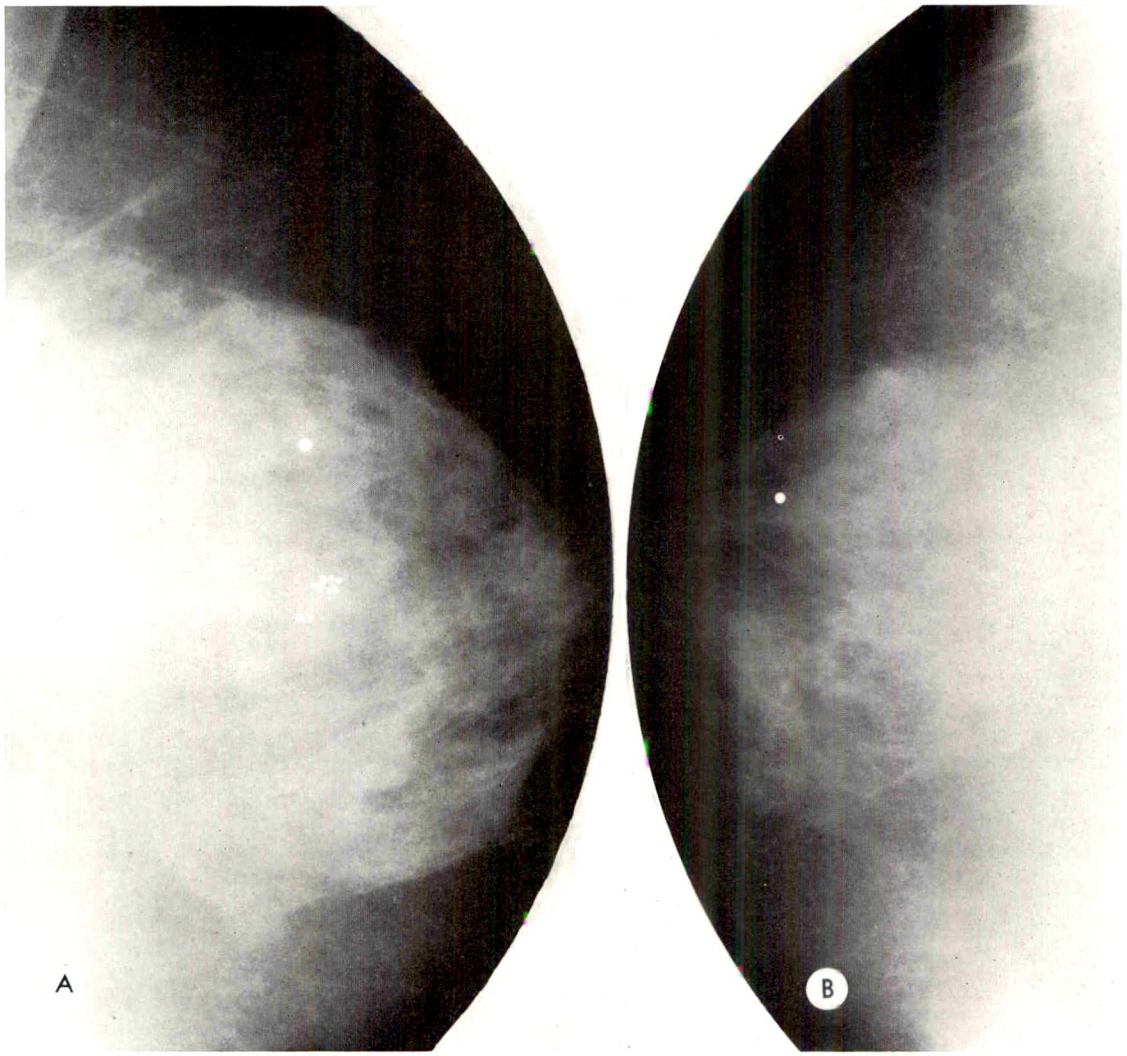


FIG. 2. (*A* and *B*) This sixty year old patient was admitted to the hospital for biopsy of a large, hard, irregular mass, regarded as malignant, in the lower inner quadrant of the right breast. The left breast was asymptomatic. A roentgenogram (*A*) revealed an extensive carcinoma containing some minute calcific deposits (semidiagrammatic) corresponding to the clinically palpable mass in the right breast. Also another carcinoma (*B*) in the left breast was found corresponding to a semilunar area of increased density with indistinct borders. The pathologist reported a scirrhous carcinoma in the left breast and a large cell carcinoma in the right breast.

truth as it pertains to some breast cancers. Because of these circumstances, delaying tactics and conservative measures too frequently seem justified by the harassed physician in the management of breast cancer. It is this sort of unfortunate attitude which has hampered the more universal introduction of roentgenography in the diagnosis and treatment of breast diseases.

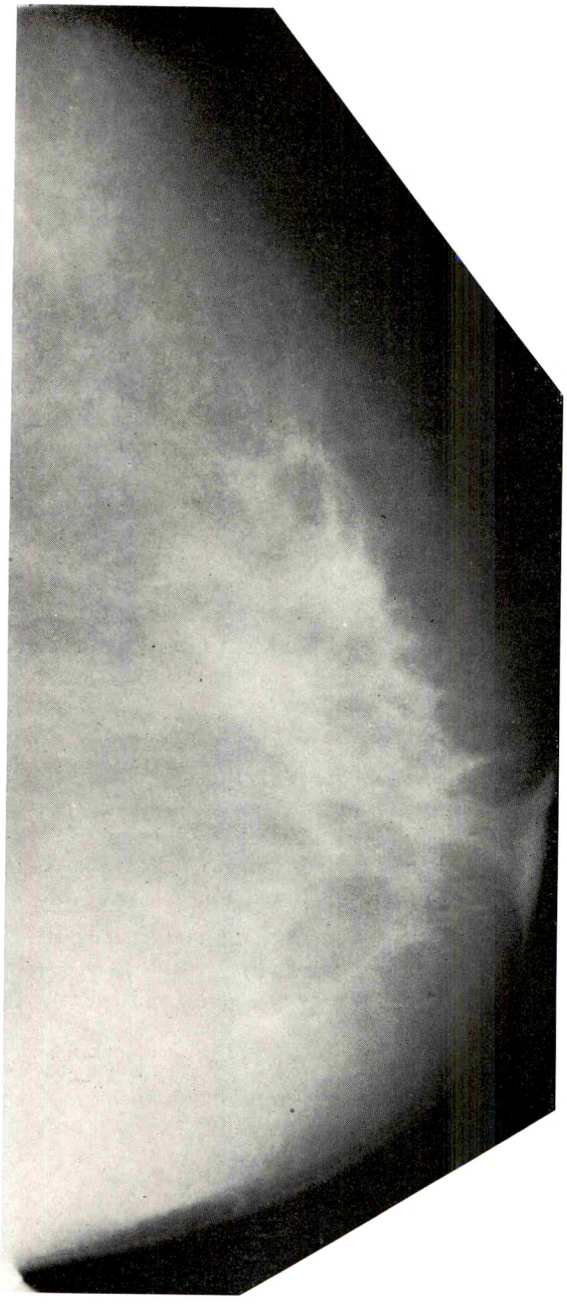


FIG. 1. This sixty-two year old patient was admitted with a movable nodule in the right breast which was believed to be a benign lesion. The mass was interpreted as a scirrhous carcinoma by the roentgenologist. The pathologist reported the presence of a large cell carcinoma with metastases to the axillary lymph nodes.

How can roentgenography *avert* delays in diagnosis and therapy? If a woman learns that she will be asked to have a roentgenographic examination before her physician concludes his final examination and if she is told that chances are better than 80 per cent that her condition is benign even before the studies are made, she is less likely to be immobilized by stark fear or the conjuring of an operation. The procedure of mammography postpones decision which allows her a temporary period of psychologic adjustment; but for the family physician, the following chain of events is set in motion. If the presence of a benign lesion is reported by the roentgenologist, two courses of action are open to him. He can accept the roentgen evidence and check the status of the lesion by properly timed re-examinations; or he can advise a diagnostic resection to which we are partial. If he asks the patient to submit to a surgical procedure, he is in a position to assure her that the roentgen findings already point to a benign condition and that the reason for the surgical interference is to secure confirmation of the diagnosis by the pathologist. He can also tell her that the likelihood of the roentgenographic report being in error is very remote and with this assurance, he is likely to find his patient more calm and acquiescent to his advice.

On the other hand, if a malignant lesion is found by the roentgenologist, the family physician is constrained to act immediately. He cannot carry on with expectant treatment in the face of so serious a diagnosis without assuming commensurate responsibility. In this manner, roentgenography serves to detect cancer and to initiate prompt action in the management of this serious disease.

ROENTGENOGRAPHY AND THE MANAGEMENT OF BREAST CANCER*

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ALTHOUGH breast roentgenography was first attempted almost fifty years ago, its adoption has been reported from few laboratories throughout the world. During the past decade at the Albert Einstein Medical Center in Philadelphia, mammography has been used routinely on almost every patient before operation. Correlation of roentgenographic and pathologic findings from whole breast sections as well as from conventional preparations was carried out with the able collaboration of Dr. Helen Ingleby.[5] It was soon learned that the roentgenographic findings were highly accurate, a conclusion now shared by many roentgenologists.[1,3,9,13] Since it is admitted that the opinion of the pathologist supersedes that of the roentgenologist, advocacy of the routine use of mammography has not been enthusiastically accepted. In practice, however, roentgenography can serve exceedingly useful purposes. Detection of early lesions and initiation of prompt surgical interference occur more regularly when roentgenography is employed for the following reasons: (1) additional information is furnished as to whether a dominant mass is benign or malignant (Fig. 1); (2) discovery is often made on roentgenograms of a carcinoma in a different portion of the breast than at the site of the dominant mass; and in 2–3 per cent, cancer is found in the opposite breast in the absence of signs (Fig. 2, *A* and *B* and 4); (3) demonstration by the roentgenologist of a malignant lesion in a multinodular breast *without* a dominant mass (Fig. 3); (4) confirmation of a benign or malignant lesion in a breast which has been previously operated (Fig. 4); (5) accurate diagnosis can be made of a breast lesion in a woman with complaints even when no positive physical findings can be elicited (Fig. 5); (6) demonstration of an occult carcinoma is possible; (7) appraisal of a lesion in a patient with cancerophobia is within the competency of the roentgenologist (Fig. 6); and (8) demonstration of a malignant lesion in a woman with no symptoms, but who is surveyed periodically (Fig. 7).

More important than these diagnostic aids is the chain of reactions initiated by the roentgenologic consultation. When a woman discovers a lump in her breast, she is frightened. The inertia which sets in depends on many factors. Women delay seeking medical advice until they have had a chance to observe the behavior of their findings for several days, weeks, months or even years. When they finally consult a physician, further postponement of appropriate therapy not infrequently occurs because of the limitations of inspection and palpation. Not all signs of malignancy are so classic as detailed in text books, and the average physician does not encounter enough cases of breast cancer to recognize those with unusual signs. Since 4 out of 5 women are apt to present themselves with benign lesions of the breast, it is difficult for a physician to maintain a high index of suspicion.[12] Other contemporary factors tend to obtund his alertness. Progressive improvement in mortality statistics has not occurred with modern surgery and radiation therapy nor has intensive propaganda to adopt self-examination made material impact; also much has been bruited about concerning "biologic predeterminism" in cancer which actually contains a grain of

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is emphasized. Squamous cell papillomatosis of the trachea should be included in the differential diagnosis of the tracheal tumors.

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We are indebted to Dr. Jerome Dubowy of the Brooklyn VA Hospital for permission to use Case III.

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tient was rebronchoscoped and tracheal papillomas which were obstructing the airway were removed. Following bronchoscopy it was difficult to arouse the patient. He was placed in a Byrd respirator. His condition temporarily improved but in spite of all efforts, he expired on the same day. At autopsy, multiple tracheal and laryngeal papillomas were found (Fig. 7). Histologic examination disclosed columnar epithelium with transition to the squamous type (Fig. 8). Some areas showed penetration of the tracheal wall and alveolar invasion was found.

DISCUSSION

It is generally believed that the diagnostic evaluation of the trachea lies in the domain of the bronchoscopist. In practice, however, bronchoscopy is reserved for those cases where tracheal or bronchial pathology is suspected. Our Case I shows quite clearly that the radiologist is often the first who is able to recognize tracheal pathology. A large percentage of the tracheal tumors in adults occurs at the upper third and therefore a lateral roentgenogram of the neck can be diagnostic (Fig. 2). Laminagraphy has been considered for many years as a very valuable roentgenologic method for the examination of the trachea. In our Case III laminagraphy showed the polypoid masses in the trachea (Fig. 6). The difficulty in laminagraphic examination is that in the presence of upper airway obstruction it is hard to get the patient's full cooperation. If the patient's condition permits, tracheography or tracheobronchography has infinite value.

Squamous cell papillomatosis of the trachea in adults apparently is very rare. To our knowledge only 3 cases have been reported in the literature.[1,16,18] Some authors believe[13] that it is potentially malignant. We found in our 3 cases that, even though these growths are histologically nonmalignant, eventually they run a very grave course and lead to the patient's demise. Following local and sometimes even more radical excision, they tend to recur. Repeated bronchoscopies are frequently required. Our Case III had 20 or more such procedures. This leads to many complications, the most severe being cerebral anoxia.

In our Case II, the bronchoscopist had the impression that he was dealing with bronchogenic carcinoma arising from the carina. Figure 4 shows that the pathology specimen itself resembled a polypoid growth. Only after repeated biopsies was the diagnosis of squamous cell papillomatosis accepted. The natural history of the squamous cell papillomatosis is not well understood. It is interesting to note that there is increasing evidence that the presence of squamous metaplasia in the bronchial tree shows close correlation with the occurrence of bronchogenic cancer.

Without attaching undue significance to it, we noted that all 3 of our cases were middle-aged Negro males, and 2 of them suffered at times from active pulmonary tuberculosis. All 3 patients were smokers.

Wheezing, dyspnea and cough were the characteristic symptoms as our patients presented themselves. Due to the fact that a large per cent of tracheal tumors occur at the upper third, it is suggested that every patient who presents with this triad of symptoms have a roentgenologic examination of the neck in addition to the conventional chest roentgenogram.

We feel that squamous cell papillomatosis should be considered in the differential diagnosis of the tumors of the trachea and major bronchi. We hope that by presenting our cases we called attention to this entity, and that more cases will be recognized and studied by radiologists, bronchoscopists and pathologists.

SUMMARY

Three proven cases of papillomatosis of the trachea are presented. The literature is briefly reviewed and the pathology is discussed. The characteristic symptoms are dyspnea, wheezing and cough. The importance of the roentgenologic study of the neck in the presence of the above symptoms

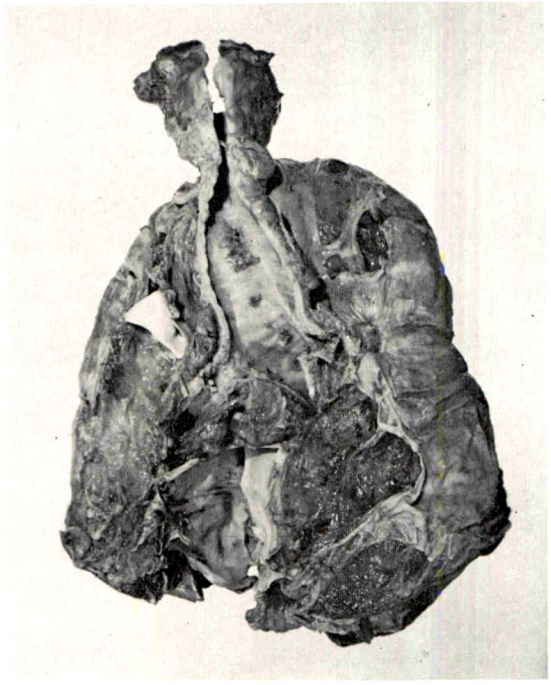


Fig. 7. Case III. Gross autopsy specimen shows multiple papillomas in the trachea extending into the bifurcation.

however, 9 months later he signed out of the hospital against medical advice.

He was re-admitted in February, 1961, with chief complaints of hemoptysis, dyspnea and weight loss. The sputum cultures for acid fast bacilli at this time still were positive. Shortly after admission the patient expired. Autopsy revealed, in addition to the advanced pulmonary tuberculosis, extensive papillomatosis of the trachea in the upper third and just above the carina (Fig. 4 and 5). Histologic examination showed squamous cell papillomas with atypical cells.

Case III. J.S., a 47 year old Negro male, was hospitalized for the first time in late 1952, because of hemoptysis, chest pain and weight loss. A chest roentgenogram showed moderately advanced pulmonary tuberculosis, and sputum culture for acid fast bacilli was positive. The patient was treated for tuberculosis and discharged in an improved condition.

The patient was re-admitted in January, 1954, with chief complaints of hoarseness and productive cough. Laryngoscopy at this time revealed multiple laryngeal papillomas which were removed. A chest roentgenogram showed a lung abscess, which was treated with antibiotics. During the year of 1954, the patient was re-admitted two more times on which occasions repeated laryngoscopies were performed and recurrent laryngeal papillomas were removed under local anesthesia.

Towards the end of 1954, the patient was re-admitted again because of pneumonia at the left base. At this admission for the first time bronchoscopy was performed, and in addition to the larnygeal papillomas multiple tracheal papillomas were noted. Laminagrams of the chest revealed a multiple polypoid mass within the lumen of the trachea (Fig. 6). From 1954 to approximately 1960, the patient was hospitalized many times. His presenting symptoms were progressive shortness of breath and hoarseness. He had approximately 20 bronchoscopies performed and recurrent tracheal and laryngeal papillomas were removed. He was maintained on antituberculous therapy intermittently and serial electrocardiograms demonstrated severe myocardial damage.

On his last admission in April, 1960, the pa-

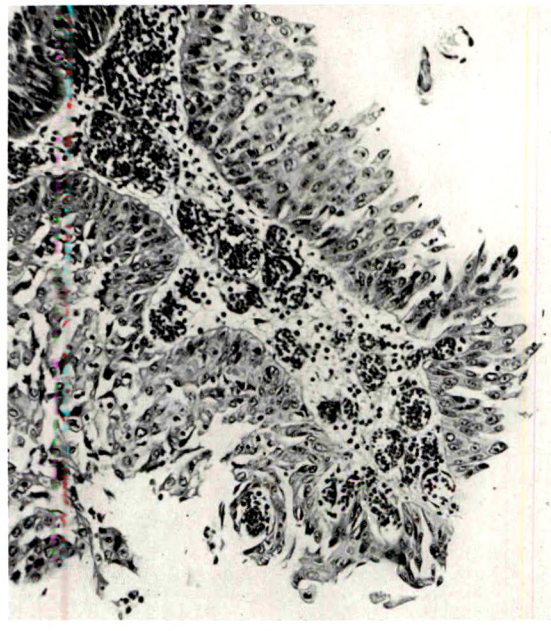


Fig. 8. Case III. Photomicrograph of a squamous cell papilloma of the trachea. The transition of columnar epithelium into squamous epithelium is well seen.



Fig. 4. Case II. Gross autopsy specimen shows papillomatosis of the trachea in the upper third and at the carina.

patient had an uneventful recovery and bronchoscopy before discharge showed no evidence of recurrence (Fig. 3).

The patient was re-admitted 4 months after the operation (February 25, 1960) with chief complaints of stridor and cough. Bronchoscopy revealed a recurrent nodule at the site of the previous operation. Biopsy was taken which showed squamous cell papilloma with atypical cells. The patient was rebronchoscoped and the papilloma fulgurated. However, it was felt that the patient should be bronchoscoped again under general anesthesia. This was performed 5 days later at which time anoxia developed which resulted in a decerebrate state. Three months later the patient expired.

Case II. A.R., a 43 year old Negro male, was



Fig. 5. Case II. Closeup of the papillomas in the upper trachea.

transferred from another hospital in January, 1956 with pneumonia and lung abscess. Bronchoscopy revealed a nodular mass just above the carina, extending into the main bronchi. Biopsy was taken and the pathologic report showed squamous cell papillomas with atypical cells. Sputum culture was positive for acid fast bacilli. The patient received therapy for tuberculosis and showed considerable improvement;

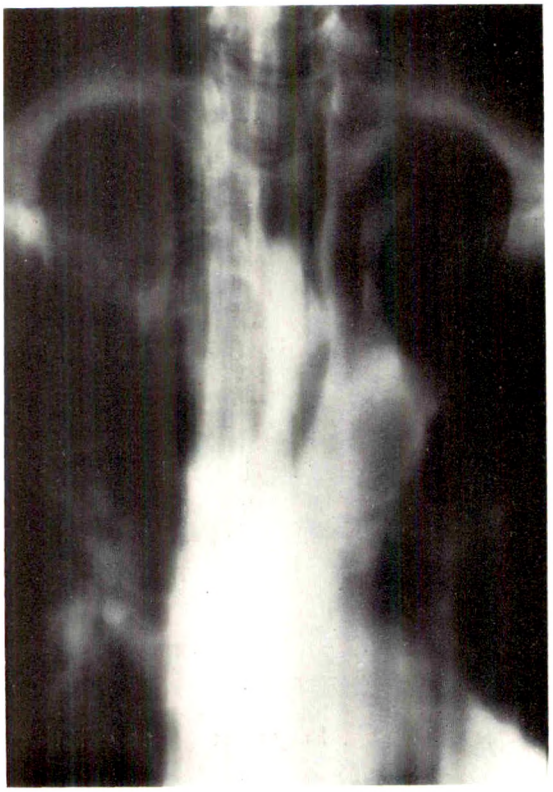


Fig. 6. Case III. Anteroposterior laminagram of the chest at the level of the trachea shows a mass density partially obstructing the trachea at the middle third.

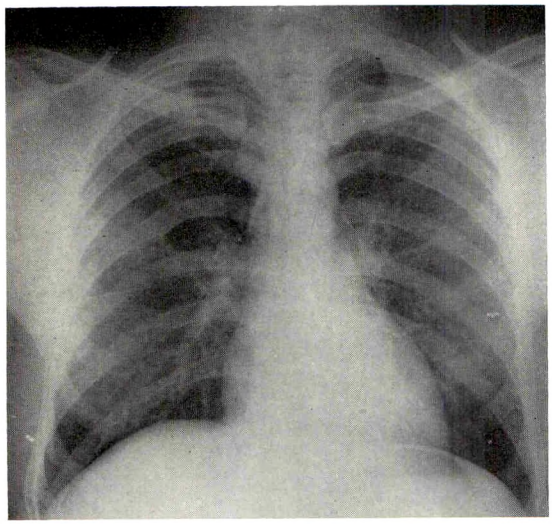


FIG. 1. Case 1. Posteroanterior chest roentgenogram shows normal appearance.

inspiratory and some expiratory stridor. A chest roentgenogram was reported as negative (Fig. 1). A lateral neck roentgenogram (Fig. 2) revealed marked narrowing of the air column in the upper third of the trachea. Only a small streak of air was visualized between the nodular soft tissue densities arising from the anterior and posterior wall. The air column below the narrowed segment and the retrotracheal space appeared normal.

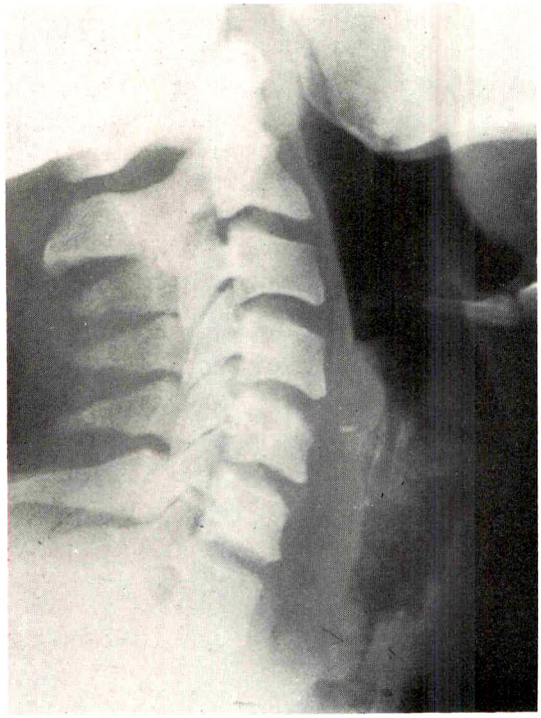


FIG. 2. Case 1. Lateral roentgenogram of the neck. Soft tissue mass densities arising from the anterior and posterior wall of the trachea, almost completely obstructing the lumen at the upper third, are visualized.

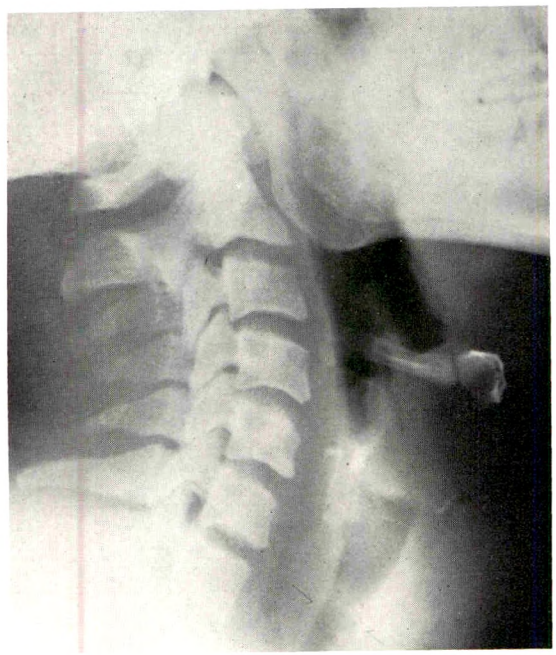


FIG. 3. Case 1. Lateral postoperative roentgenogram of the neck still shows some narrowing of the trachea at the site of the operation. The airway shows considerable restoration.

On the following day bronchoscopy revealed polypoid soft tissue masses, about 5 cm. below the vocal cords, between the second and fifth tracheal rings. These masses were soft, white to yellow in color and seemed to bleed easily. Biopsy was taken and tracheostomy performed. The pathologic report showed squamous cell papillomas with atypical cells.

On October 22, 1959, tracheal exploration was performed, and multiple soft, friable lobulated pinkish papillomas were found arising from the mucosa of the trachea. There was no evidence of extension into the wall. The mucosa of the involved segment of the trachea was stripped and the site of the papillomas was cauterized. The

PAPILLOMATOSIS OF THE TRACHEA AND BRONCHI*

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PAPILLOMATOSIS of the trachea is rare in adults but not uncommon in children. When compared to other tumors of the trachea, the incidence is very low.

The object of this paper is to present 3 proven cases of papillomatosis of the trachea and bronchi in adults and to stress the importance of a lateral soft tissue examination of the neck.

REVIEW OF LITERATURE

The occurrence of papillomatosis of the trachea in adults is difficult to assess. D'Annoy and Zoeller[3] found 59 cases of tracheal papillomas in the world literature. They, however, excluded papillomatosis of the trachea on the basis that they were not considering it as a primary tumor. All authors tend to agree that papillomatosis in childhood is a relatively common occurrence and has a fairly good prognosis.[3,5,9,11,12,13,15]

Rosenberg found in children 16 cases of papillomas out of 5,808 bronchoscopic examinations and Schrotter found 10 out of 7,324 examinations.[7] Jackson and Jackson[8] feel that papillomatosis of the trachea in childhood is ultimately a self limiting disease, and at the time of bronchoscopic removal it is unwise to deal radically with the base since these tumors may appear in new, even remote locations. Gilbert *et al.*[5] found an incidence of 56 per cent of papillomas out of 39 cases of tracheal tumors in infants and children. In spite of the general favorable prognosis in childhood, several fatal cases have been reported.[6,7]

A case of simultaneous laryngeal, tracheal and bronchial papillomatosis in an adult patient who had a 20 year follow-up was reported by Buffmire *et al.*[1] They feel that this entity is very rare. The papillomas were probably of multicentric origin, rather than the result of aerial metastasis. Zamora[18] and Syme[16] have reported cases in which after repeated bronchoscopic removal, the papillomata ceased to reappear.

PATHOLOGY

Papillomas of the trachea are characterized by multiple flat small nodular masses that primarily involve the mucosa (Fig. 4 and 5). They may be discrete or coalescent and may involve a large area of the trachea. The larger masses may invade the tracheal wall but usually are superficial and limited to the mucosal portion. They are covered by respiratory epithelium and in most instances contain atypical cells (Fig. 8). They present a core of connective tissue surrounded by spindle cells which show squamatization. In adults the papillomas are usually single and tend to infiltrate and may metastasize; they are potentially malignant. In children they are multiple and tend towards regression; they do not have the potential of becoming malignant. The multiple papillomas may extend into the main stem bronchi and in some instances into the segmental bronchi. Following surgical removal they have a tendency to recur not only locally but to extend up and down the trachea and into the bronchi.

REPORT OF CASES

CASE 1. D.P., a 37 year old Negro male, entered the hospital for the first time on September 25, 1959, with chief complaints of shortness of breath, wheezing and a cough which had become increasingly worse in the past 3 months. Physical examination including indirect laryngoscopy revealed no abnormality except marked

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viduals. However, the overwhelming majority of cases has been in adolescents or young adults. Kerwin[7] claims that angiofibromas arise only in young patients and show regression with age.

Tumors involving the sphenoid sinus are uncommon. The only primary neoplasm described has been a very rare carcinoma. Secondary invasion by meningiomas and osteomas has been noted.[11]

It is generally agreed that the initial symptom is usually nasal obstruction with epistaxis occurring later. Härmä,[5] reviewing 52 cases in 1958, found this to be true. Several authors have reported paranasal sinus invasion, predominantly antrum, but no reported cases of sphenoid sinus involvement could be located. Sternberg[13] reported 2 cases presenting with exophthalmos. Massoud and Awwad[9] reported 7 cases with a variety of symptoms which occurred in combination with nasal obstruction and epistaxis. They claimed, in contradiction to most other authors, that this tumor can metastasize. In one of their cases, the lesion extended to the pituitary fossa, but without accompanying symptoms. Hubbard[6] implies that malignant transformation may be possible, and Batsakis and his coworkers[2] noted a case of fibrosarcoma occurring following surgery and irradiation of an angiofibroma. It is of interest that their patient was 54 years of age.

The differential diagnosis usually concerns nasal polyps and inflammatory tissue. An angiofibrosarcoma must be considered and the chest checked carefully for metastases. In our case, a sphenoid meningioma, pituitary tumor or chordoma were definite clinical possibilities, but ruled out histologically.

CONCLUSIONS

A case of nasopharyngeal fibroma occurring in a 50 year old woman is reported. This tumor extended into the sphenoid sinus, involved the pituitary fossa and optic nerves and caused symptoms of excessive thirst and partial loss of vision.

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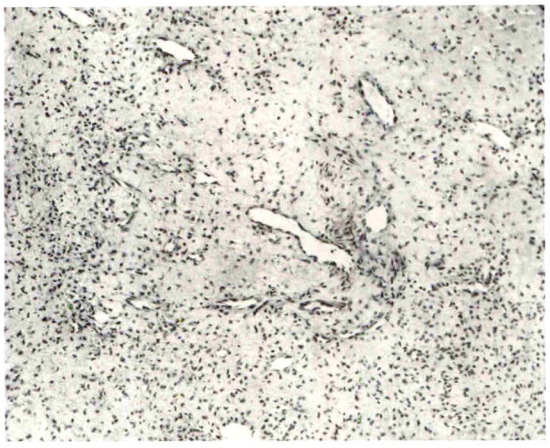


Fig. 5. Typical area of histologic specimen showing the fibrous tissue with a minor vascular component.

to 105°F.; she remained comatose and died the following day.

Autopsy, limited to the brain, revealed the fibrous tumor, which extended from the nasopharynx and sphenoid sinus into the sella turcica. It had undergone extensive myxomatous degeneration.

Upon review of the biopsy and autopsy material, the fibrous nature of the tumor was beyond question.* There was a vascular component, but it was minor and for the most part nonproliferative. There were no cells of neurogenic or pituitary origin nor was there any suggestion of malignancy.

DISCUSSION

Most authors do not differentiate between fibromas and juvenile angiofibromas of the nasopharynx. Ash and Raum[1] believe that this tumor in young individuals is primarily vascular and shows active growth. Furthermore, they think that it becomes more fibrous with age and that it tends toward spontaneous regression at approximately 25 years of age.

Ward and Hendrick[14] consider these tumors benign, nonmetastasizing, but growing and destroying by direct extension. If excised, they frequently recur. Erosion of the mucous membrane causes the tumor to ulcerate and produce epistaxis as the initial symptom.

The origin of this tumor is widely debated. The currently accepted theory is that it arises from embryonic fibrous tissue of the sphenoid or occiput or from the upper cervical vertebrae. Schiff[12] believes that this tumor is due to an alteration in the pituitary androgen-estrogen axis, involving pituitary overactivity and a vascular ground-substance response. An endocrine theory of origin previously had been considered by a number of other workers.

Osborn[10] states that this lesion represents not a tumor, but a vascular malformation with changes secondary to hemorrhage. He considers the tissue "erectile" in nature with an increase in size at puberty and hemorrhage due to thin walls.

Another moot point concerning this tumor is its age-sex predilection (Table 1). Martin and his associates[8] claim that it does not occur in females. The majority of reports in the literature seems to bear this out, but Figi[3] in 1940 reported 5 cases in females and Handousa and Elwi[4] in 1954 found 11 females with this lesion. In reviewing 70 cases, Handousa and Elwi do not accept the hormonal theory and call the nasopharyngeal fibroma a true neoplasm rather than a malformation. In addition, they find that it does occur in older indi-

Table I

Author	Date	Age of Patients	Male	Female
Figi[3]	1940	10 to 31	58	5
Martin and co-workers[8]	1948	7 to 19	29	
Handousa and Elwi[4]	1954	6 to 50	59	11
Sternberg[13]	1954	9 to 27	25	
Härmä[5]	1958	10 to 25	52	
Hubbard[6]	1958	9 to 50*	26	
Massoud and Awwad[9]	1960	21 to 25	7	

* The microscopic pathology was reviewed by Dr. Bernard Alpers, Chairman of the Department of Neurology, Jefferson Medical College Hospital, and Dr. Simone Soumeral of the Jefferson Medical College Hospital Department of Pathology.

* Hubbard reported one case of a 50 year old man, whose initial symptoms occurred at age 13. He was treated and the tumor recurred 37 years later following trauma. Otherwise, the oldest patient in his series was 27.

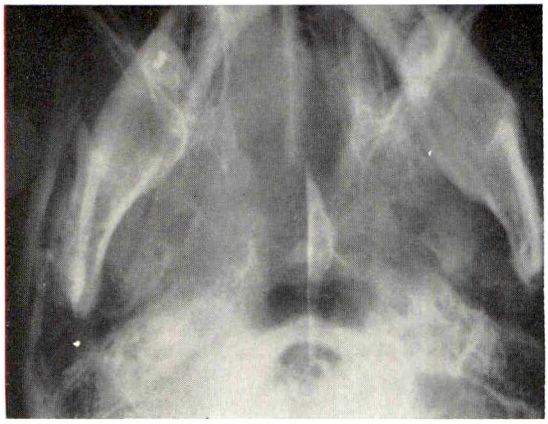


FIG. 2. Base view showing destruction by tumor mass on right.

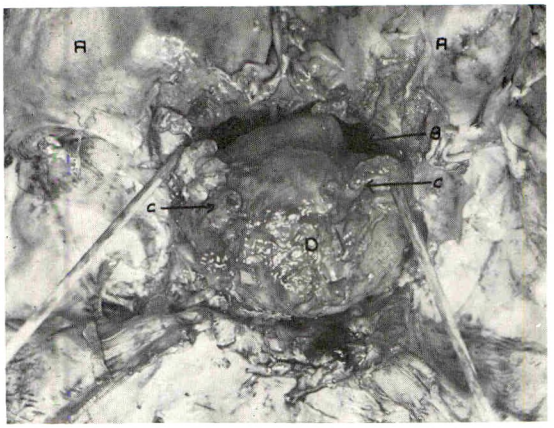


FIG. 3. Gross specimen at autopsy. A. Anterior fossa; B. pituitary fossa; C. carotid arteries; D. tumor.

of contrast material into the sphenoid sinus was unsuccessful.

On January 7, 1958, the patient wax transferred to the Otolaryngology Service and returned to the operating room, where by transseptal approach, a mass was found in the posterior pharyngeal wall and sphenoid sinus. Biopsy revealed an "infiltrating angiofibroma." Following this procedure, the patient developed a staphylococcal meningitis and became comatose. Under an appropriate antibiotic regimen, she made a gradual recovery.

On March 18, 1958, the patient was referred to the Radiation Therapy Department and accepted for cobalt 60 beam therapy. She was treated by 210° arc rotation of the pituitary fossa, sphenoid ridge and nasopharynx, utilizing a 6×6 cm. beam to a dose of 6,130 r to the tumor in 6 weeks. Her treatment was completed on April 29, 1958, with marked improvement in her general condition and visual field defects. She was followed regularly for 6 months and remained well except for some weight increase. She then failed to return for a year and was readmitted on November 13, 1959 in a semicomatose condition.

On examination, she was agitated and responsive only to painful stimuli. Facial hirsutism was again noted. Her temperature rapidly rose

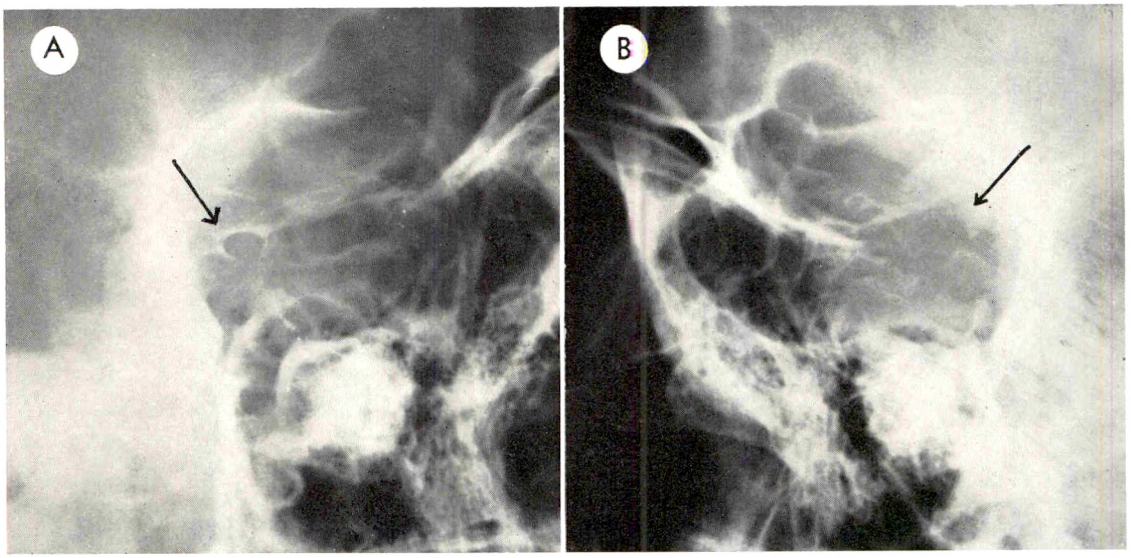


FIG. 4. Normal left optic foramen seen in *A*. Destroyed right optic foramen seen in *B*.

A NASOPHARYNGEAL FIBROMA PRESENTING WITH PITUITARY AND OPTIC NERVE SYMPTOMATOLOGY

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FIBROMAS or juvenile angiofibromas of the nasopharynx have previously been reported as presenting almost exclusively with nasal obstruction or epistaxis. They have been found predominantly in adolescent and young adult males. The following case report is unusual because of the patient's age, sex and initial symptoms.

REPORT OF A CASE

The patient (V.R.), a 50 year old white female, was admitted for the first time on December 23, 1957 to the Jefferson Medical College Hospital Neurology Service with the chief complaint of poor vision. Four months prior to admission, she noted polydipsia, up to three quarts of liquids per day, and polyuria. Two months before admission, she experienced increasing loss of visual acuity, predominantly in the right eye. She denied headaches, convulsions, abrupt change in weight or menstrual abnormalities. There was no history of nasal obstruction or epistaxis. The previous medical history was essentially negative.

On physical examination, she was found to be an obese female in no distress. The blood pressure was 140/90, pulse 80 and respirations 20. She was hirsute but denied any change in hair pattern since adolescence. There were minimal proptosis and slight outward rotation of the right eye. The right pupil was slightly larger than the left and both reacted to light and convergence. There was limitation of inward and upward gaze in the right eye. Ophthalmologic consultation revealed paresis of the right inferior rectus and right inferior oblique muscles. In addition, there were bilateral inferior visual field defects. Pallor of the right optic disk was also noted. The remainder of the neurologic and general physical examination was not remarkable.

On admission, a complete blood cell count and urinalysis were normal. The fasting blood glucose was 80 mg. per cent, blood urea nitrogen 12 mg. per cent, and an electrolyte profile was normal. The protein bound iodine was 3.3 μg. per cent.

A roentgenogram of the chest was normal. Skull roentgenograms revealed destruction of the dorsum sellae with widening of the sella turcica. The right anterior clinoid process appeared entirely destroyed and the left partially so. Special views of the optic foramina revealed destruction of the entire right optic foramen and portions of both sphenoid wings. A right carotid arteriogram demonstrated uncoiling and superior displacement of the siphon. A left arteriogram was not carried out.

On December 27, 1957, a right frontal craniotomy was performed. Exploration of the anterior fossa disclosed flattening of both optic nerves. A small area of hyperemia was noted in the dura, medial and anterior to the right optic nerve. This area extended posteriorly into the sella turcica. It was felt that there was an extradural mass expanding into the sphenoid sinus and sella turcica. No attempt at biopsy was made at this time.

The patient's postoperative course was benign except for a single Jacksonian seizure on the sixth postoperative day. Consultation with the Otolaryngology Service revealed that a questionable mass was present in the posterior nasopharynx. An attempt at trochar instillation

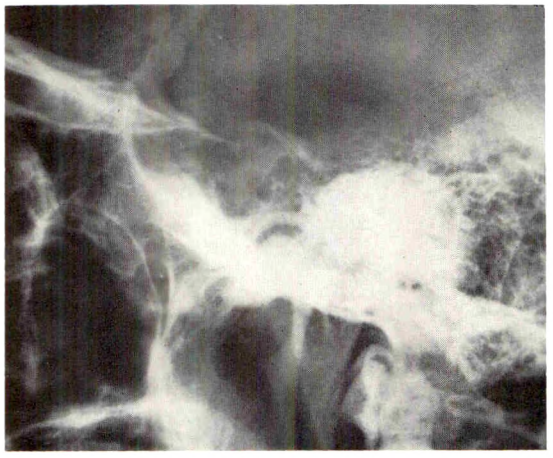


FIG. 1. Magnified view of sella turcica area showing invasion and destruction of the sphenoid sinus and the sella turcica.

TABLE IX

DATA FROM THE CALIFORNIA TUMOR REGISTRY OF NASOPHARYNGEAL TUMORS TREATED AT THE LOS ANGELES TUMOR INSTITUTE FROM 1942–1952

Total no. of cases	33	
Loss to follow-up	3	
Determinate cases	30	
Survival rate: Absolute, all stages, types, treatments, etc.		
3 yr. survival	2 (6.7%)	
5 yr. survival	1 (3.3%)	last follow-up 1957—alive 14 yr.

The results from other institutions show an average of 25–30 per cent 5 year survivals, ranging from the low reported by Geist and Portmann[6] of 10 per cent to a high of 36 per cent reported by Smedal and Watson,[13] using supervoltage therapy. The results of our study compare favorably with those reported in the literature.

SUMMARY

Forty patients with histologically proven malignancies of the nasopharynx were treated and followed at the Los Angeles Tumor Institute during the period of 1951–1960. Using the 2 mev. Van de Graaff electrostatic generator, 6,000 r tissue dose was delivered to the nasopharyngeal area and to the pathway of the lymphatic drainage in an average treatment time of 6–8 weeks. Patients included new cases and treatment failures being re-treated. Twenty-four cases were followed for 5 years and the survival rate was 8 out of 24 (33 per cent) for the over-all group; however, using supervoltage therapy alone there was a 5 year survival of 4 out of 9 cases (44 per cent). An additional 4 cases have been followed for only 4 years and, if these are included, the 4 year survival is 8 out of 13 (61 per cent).

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TABLE V

EFFECT OF CERVICAL LYMPH NODE METASTASES ON SURVIVAL

	No. of Patients	3 yr.	No. of Patients	5 yr.
Unilateral involvement of cervical lymph nodes	11	8 (72%)	8	5 (62%)
Bilateral involvement of cervical lymph nodes	8	3 (37%)	8	1 (12%)
Metastases to base of skull	4	1 (25%)	4	1 (25%)

per cent). When Group 1 is considered, the 5 year survival is 6 out of 7 patients (86 per cent). These results are higher than most of those reported in the literature. One patient survived 13 years after combined therapy, expiring from radiation necrosis of the base of the skull with secondary meningitis. The cases of epidermoid carcinomas did rather poorly and only 2 out of 15 patients (14 per cent) survived 5 years. Little improvement is noted in the Group 1 series. Two cases of rhabdomyosarcoma in children had a progressive downward course and expired with disease in 1 year and 2 years, respectively. Radiation showed little significant effect.

In Table v the effect of metastases on survival is shown. Five patients out of 8 with presenting signs of unilateral cervical lymphadenopathy survived 5 years (62 per cent) while only 1 patient out of 8 with bilateral cervical lymphadenopathy survived 5 years (12.5 per cent).

Of more significance is the survival according to the clinical staging (Table VI). The 5 year survival for Stage 1 is 4 out of 5 (80 per cent), for Stage 2, 7 out of 21 (33 per cent), and for Stage 3, 1 out of 5 (20 per cent).

The effect of the duration of symptoms on survival is shown in Table VII.

The most common cause of death in our series was brain metastasis or direct invasion of the skull (45 per cent) while generalized dissemination was the second most common cause (37 per cent) (Table VIII).

A comparison with the results of treatment of patients with nasopharyngeal carcinomas at the Los Angeles Tumor Institute from the period of 1941–1951 as shown in the California Tumor Registry reveals a survival of 1 patient out of 30 determinate cases (3 per cent). This case has been followed for 14 years without evidence of recurrence (Table IX).

TABLE VI

EFFECT OF STAGE OF DISEASE ON SURVIVAL

	No. of Patients	3 yr.	5 yr.
Stage 1	5 (16.5%)	5 (100%)	4 (80%)
Stage 2	21 (67.0%)	10 (47%)	7 (33%)
Stage 3	5 (16.5%)	3 (60%)	1 (20%)

TABLE VII

EFFECT OF DURATION OF SYMPTOMS ON SURVIVAL

	No. of Patients	3 yr.	5 yr.
Less than 1 yr., ave. 3.5 mo.	18	11 (61%)	7/12 (41%)
More than 1 yr., ave. 2.5 yr.	4	3 (75%)	2/3 (66%)
Not recorded	9	—	—

TABLE VIII

CAUSE OF DEATH IN 27 DETERMINATE CASES

Generalized disease	10 (37%)
Brain involvement	12 (45%)
Meningitis	1—expired 13 years after treatment
Mediastinitis, postoperative	1—expired within 6 mo. after treatment with disease
Cirrhosis	1—NED* at death, 2 yr. after treatment
Pneumonia	1—NED* at death, 5 yr. after treatment
Cerebral vascular accident	1—NED* at death, 6 mo. after treatment

* NED—No evidence of disease.

Table II

OVER-ALL 3–5 YEAR SURVIVALS

Absolute survival—all patients considered		
3 year survival	18 (58%)	
5 year survival	8 (33%)	4 patients alive 4 yr. with NED* not included

* NED—no evidence of disease.

inclusion in the survival study. Of these, 3 patients died of disease, another died of a cerebral vascular accident without evidence of disease, and the remaining 5 are alive without evidence of disease, 2 for 2 years and one each for 10 months, 9 months and 5 months. No cases were lost to follow-up.

The absolute survival rate for all cases, including those with initial therapy and those re-treated for recurrences or metastatic disease, is shown in Table II. Eighteen out of 31 (58 per cent) survived 3 years while 8 out of 24 patients (33 per cent) survived 5 years. Two patients died from other causes and showed no evidence of disease, one at 2 years from cirrhosis and the other at 5 years from pneumonia.

The series was divided into Group I, which consisted of 15 patients who received initial 2 mev. therapy and Group II, with 14 patients who received combined therapy for recurrences as shown in Table III. In the determinate cases receiving 2 mev. radiation alone, 4 out of 9 (44 per cent) survived 5 years. This latter figure does not include 4 patients who are 4 year survivors without evidence of disease. If they are included,

Table III

SURVIVAL OF PATIENTS BASED ON MODE OF TREATMENT

Group I. 2 mev. therapy only (excluding 2 patients dying of other causes)		
3 year survival (15)	10 (67%)	
5 year survival (9)	4 (44%)	4 patients alive 4 yr. with NED* not included†
Group II. Combined therapy for recurrences or metastases		
3 year survival (14)	8 (57%)	
5 year survival (13)	4 (31%)	

* NED—no evidence of disease.
† Group I, 4 year survival 8 out of 13 patients (61%).

the 4 year survival for Group I is 61 per cent.

The patients in the combined therapy group admittedly are not expected to do as well as those receiving treatment initially with 2 mev. due to the fact that they are treatment failures at the start; however, there was a 5 year survival rate of 4 out of 13 (31 per cent). While the figures are not considered statistically significant because of the small number of patients, they do show a general trend.

Table IV gives the results based on histopathologic classification in an effort to compare relative survival times. By inclusion of the anaplastic carcinomas in the lymphoepithelioma group as suggested by Murphy,[11] the results are impressive. There is a 5 year survival of 8 out of 11 patients (72

Table IV

EFFECT OF HISTOPATHOLOGIC DIAGNOSIS ON SURVIVAL

	Over-all			Group I		
	No. of Patients	3 yr.	5 yr.	No. of Patients	3 yr.	5 yr.
Epidermoid carcinoma	16	6 (43%)	2 (14%)	9	4 (44%)	2 (22%)
Lymphoepithelioma	15	10 (91%)	8 (72%)	7	7 (100%)	6 (86%)
Rhabdomyosarcoma	2	—	—	2	—	—
Lymphosarcoma	2	Indeterminate				
Reticulum cell sarcoma	1	Died with generalized spread at 4 yr.				
Transitional cell carcinoma	1	Died with brain involvement at 3 yr.				

ance for direct spread is through the basilar foramen of the skull into the middle cranial fossa. The extension in the cranial cavity is usually extradural and symptoms are due to the tumor mass compressing the cranial nerves or encircling the structure without direct invasion.[8]

During the period of 1951–1960, 40 patients were treated with 2 mev. therapy (Van de Graaff) at the Los Angeles Tumor Institute (Fig. 1). All cases were histologically proven; only 2 patients (5 per cent) required more than one biopsy, each requiring 2. There were 29 males (72.5 per cent) and 11 females (27.5 per cent) or a ratio of 2.1 : 1, which is in close agreement with that reported in the literature. The average age at admission was 51.8 years; the youngest patient was 4 years of age while the oldest was 86 years of age. The series included 4 Chinese (10 per cent). Epidermoid carcinomas comprised the largest group of cases (47.5 per cent), while the anaplastic carcinomas and lymphoepitheliomas formed the second largest group (37.5 per cent). There were only 2 cases of lymphosarcoma and 1 of reticulum cell sarcoma. The average duration of symptoms was 3.5 months when present less than a year and 2.5 years when present more than a year.

MODE OF THERAPY

The planned course of therapy was to deliver 6,000 r to the mid-line within a 6–8 week period by lateral opposing ports extending from the level of the base of the skull to the supraclavicular region and posteriorly to the mid-portion of the neck anterior to the spinal column. If necessary to obtain the mid-line dose required, an anterior nasopharyngeal port was employed, using lead shields to block the eyes. The portal area covered was checked with localization roentgenograms taken with the 2 mev. machine, with the patient in the original set-up on the initial day of therapy and any adjustment of the field size deemed necessary was made early in the treatment. Mid-way through the treatment, re-check portal roentgenograms were taken where indicated to ensure complete coverage of the tumor bed and to observe the progressive reduction of the size of the mass. The cervical lymph nodes were routinely included in the ports, whether or not palpable disease was present, because of the high incidence of spread to these sites.

Severe skin reactions were rare. In no cases were signs of myelitis[5] noted during the follow-up period. Transient pharyngitis, glossitis, and esophagitis with anorexia and vomiting were not uncommon at about the mid-way point of the treatment and, when necessary, a rest period of 1–2 weeks was prescribed until the symptoms abated. Leukopenia also was not uncommon but not severe enough to halt treatment. Parotitis was moderately discomforting at the mid-point of therapy. Other complications found on long follow-up were muscle contractions and temporomandibular joint fibrosis. All cases received a full course of treatment, except those which were considered terminal at the time of the initial visit to the Tumor Institute. In these cases only palliative therapy was administered, usually without noticeable beneficial effects.

Cases treated for recurrence were given 6,000 r through the previously irradiated fields but in a somewhat guarded manner, with close observation for untoward, excessive skin reactions. The results were gratifying in the majority of these cases.

Of the 40 patients treated, 31 patients were considered as determinate for survival studies for a 3 year evaluation and 24 for a 5 year evaluation (Table 1). Nine patients have not been followed long enough for

TABLE I

NASOPHARYNGEAL TUMOR CASES TREATED AT THE LOS ANGELES TUMOR INSTITUTE FROM 1951–1960

Undeterminate cases	9
Determinate cases	31
3 year survival	31
5 year survival	24
Total cases	40

Squamous cell carcinomas may cause early symptoms of bleeding, nasal obstruction and dull pain in the pharynx with early invasion of the skull, while the primary growth of a lymphoepithelioma in the nasopharynx may appear long after the occurrence of bilateral cervical lymphadenopathy.[11] Lymphosarcomas usually cause obstructive symptoms early and produce massive cervical lymphadenopathy with widespread distant dissemination.

The gross pathologic appearance includes an ulcerative form, most frequently seen on the posterior wall of the nasopharynx or deep in Rosenmüller's fossa; a lobulated form, most frequently noted near the eustachian tube with occasional ulceration or such rapid growth as to cause nerve compression; and the exophytic nonulcerative form, usually observed on the roof of the nasopharynx but often filling the entire cavity and frequently involving the maxillary sinuses and orbits.

The metastatic extension of the tumor is to the regional lymph nodes, with signs and symptoms compatible to the area involved. The earliest metastatic nodal involvement may be to the Krause group of lymph nodes near the nerve exit from the jugular foramen, resulting in nerve deficit or paralysis of the ninth, tenth, eleventh and twelfth cranial nerves. The direct extension to the petropharyngeal lymph nodes and the posterior and lateral pharyngeal wall produces the petrosphenoidal syndrome of Jarod with diplopia and internal strabismus. Extension to the retroparotid space of Villaret may occur. Due to the anatomy of the nasopharynx, which is bounded by bone and taut fascia, the direction of least resist-

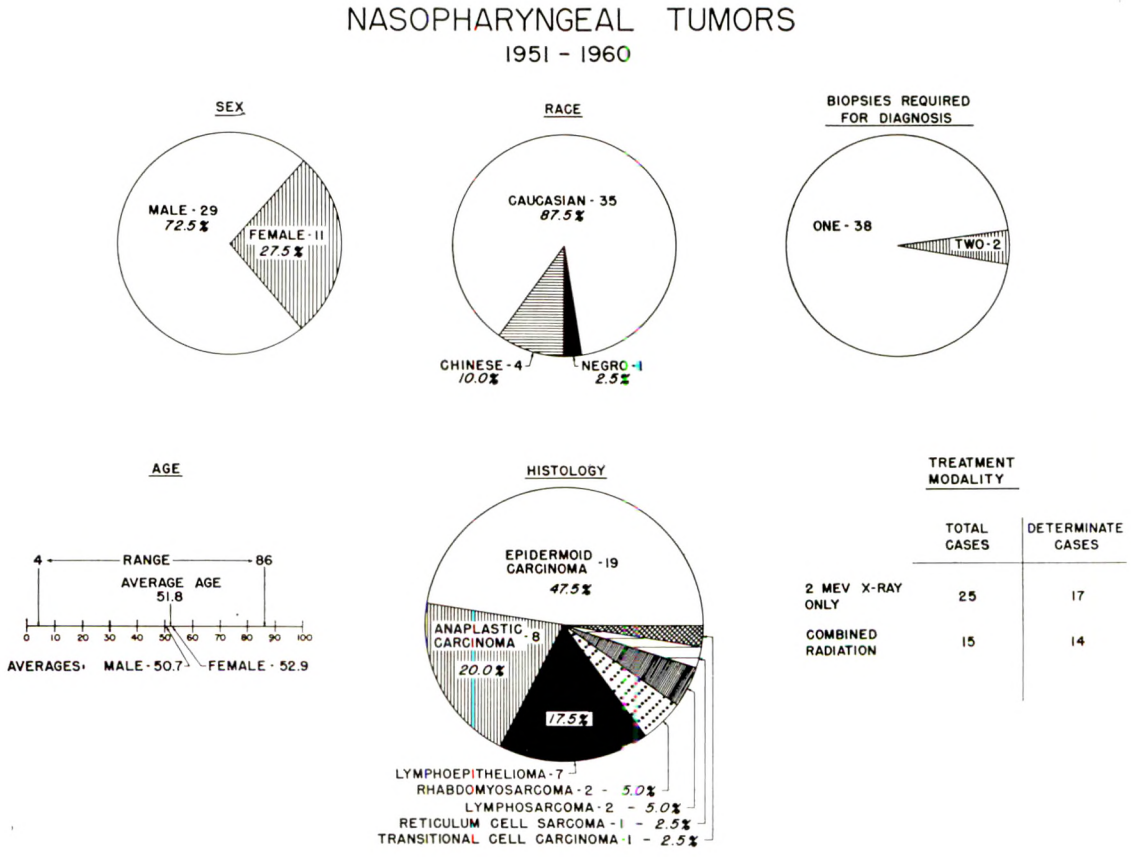


Fig. 1. Data concerning treatment series of 40 patients.

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NASOPHARYNGEAL TUMORS: THREE TO FIVE YEAR SURVIVALS*

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LITTLE has appeared in the American literature during the past few years concerning the results of supervoltage therapy for malignant tumors of the nasopharynx. A brief review of the world medical literature for the period preceding the era of supervoltage machines shows the appalling need for improvement in this field of therapy. Surgical treatment of these neoplasms yields poor results because of the wide extent of the disease at the time of the initial diagnosis in the majority of the cases. This has been pointed out by many authors and little advance has been made in the earlier diagnosis of these tumors due to their insidious growth and lack of early symptoms. Cantril's statement of the nasopharynx being a "diagnostic blind spot" remains valid today.

In view of the need for evaluation and assessment of radiation therapy periodically, a group of patients with nasopharyngeal tumors treated at the Los Angeles Tumor Institute from the time of the installation of the 2 mev. apparatus (1951) was appraised so that the results could be compared with our previous results. An effort is being made to try to find out where our failures occur and what might be done to improve the results.

Nasopharyngeal tumors are, by no means, rare and comprise 1–2 per cent of all malignant tumors of the body and approximately 18 per cent of all tumors of the head and neck.[15] The increased incidence of nasopharyngeal tumors in the Chinese has been reported in the literature by many authors.[3] The age incidence shows a preponderance in the middle-age group in the range of 40–60 years, while the sex distribution indicates a 2:1 or 3:1 ratio of men to women. It has been reported that this condition sometimes requires as many as seven biopsies over a long period of time before the correct diagnosis is obtained.

According to Ackerman and del Regato,[1] lymphosarcoma constitutes one-third to one-half of the cases. The vast majority of the remaining cases fall in the lymphoepithelioma group, comprising undifferentiated epidermoid carcinomas, transitional cell carcinomas or lymphoepitheliomas and even lymphosarcomas. Differentiated epidermoid carcinomas are rare. Murphy,[11] however, states that differentiated squamous cell carcinomas comprise approximately 40 per cent of the cases and the anaplastic squamous cell carcinomas only 10 per cent. There are still various opinions as to the validity of the histologic diagnosis of "lymphoepithelioma" of Regaud and Schmincke, but the trend seems to be in favor of this diagnosis since these cases differ in both clinical symptoms and in the response to treatment, suggesting a definite clinical entity.[8] From 31 detailed necropsies, Teoh[14] concluded that the lymphoepitheliomas are actually epidermoid carcinomas of the nasopharynx with lymphoid elements normally present. It is considered by some that the variation is merely a difference in nomenclature and description, while others feel that these are two separate tumor processes in the same location. The subject needs further elucidation before a definite conclusion can be made.

Although the variation in the histologic type reportedly leads to different symptoms early in the malignancy, metastatic lymphadenopathy is usually present with every tumor of the nasopharynx and in many instances is the reason which induces the patient to seek medical advice.[1]

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The former occurs not infrequently during treatment in the form of a mild edema of the vestibular mucosa (false cord and/or arytenoid region) without impairment of motion. It alerts us to close daily observation and, with proper adjustment of treatment, usually subsides as treatment progresses and is then of no prognostic importance. Of serious concern, however, is the late edema which occurs 2 to 3 months after completion of treatment, following an interval when the larynx seems to be intact. It particularly involves the arytenoid and aryepiglottic regions, causing fixation. It occurs in our experience only in patients who have shown a marked early reaction with a thick, confluent false membrane. In such instances, it may be impossible to decide whether the edema represents postradiation edema only or whether it is an indication of uncontrolled submucosal carcinoma. In patients with only mild, or no early mucosal reaction, it must be interpreted as due to uncontrolled disease. This late postradiation edema has occurred in 4 of the 7 patients in Group 1. In 2 of these, temporary tracheostomy was necessary. These patients are now living $4\frac{1}{2}$ years after treatment with marked radiation changes of the mucosa (severe laryngitis sicca in one instance), sufficient to suggest that laryngectomy would have been preferable even if the carcinoma seems to be controlled.

In contrast, such late postradiation edema has been seen in only 1 of 21 patients in the second group. It occurred 10 months after treatment, following an upper respiratory infection, and subsequently subsided. This patient has remained well for 1 year and 8 months. In 2 instances laryngofissure and cordectomy for radiation failure, 9 and 10 months after therapy, respectively, were tolerated without surgical complication (1 is included in Table 1; 1 was treated in 1961 and is not included in this series).

There can be no doubt that with adequately protracted supervolt therapy carcinoma of the vocal cord can consistently be treated without, or with only minimal, mucosal reaction and morbidity, and—as far as the present short-term observations indicate—without jeopardizing the initial effect on the tumor: 8 of 9 Stage 1 carcinomas and 7 of 12 Stage II lesions have so far remained controlled for periods of 14 to 39 months. It is, of course, too early to determine conclusively at this time whether the 5 year results will compare as favorably with those obtained with more aggressive techniques. In our experience, however, it is quite unusual to observe later recurrences in instances in which the larynx appears entirely normal one year after therapy.

SUMMARY

Twenty-one patients with carcinoma of the vocal cords were treated at the University of California Hospitals, San Francisco, using 1 mev. irradiation and a protraction of the over-all treatment time of 7 weeks for 5,500 r midline dose, or 6,000 r in 8 weeks (*an average of 53 days for 6,000 r*), instead of the previously used average protraction of 40 days for 6,000 r. With the longer protraction, morbidity was markedly reduced: *formation of a false membrane and the previously not uncommon late edema were not observed.* Eight of 9 patients with Stage 1 and 7 of 12 patients with Stage II carcinomas so far remain controlled with normal larynx for $1\frac{1}{2}$ to 4 years. In this series, cordectomy was done once for radiation failure; laryngectomy 4 times without surgical complications.

Although 5 year results are not yet available, observations to date indicate that the tumor effect is not jeopardized by such protraction, while subjective morbidity and tissue injury are significantly reduced.

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satisfactory,[6] but, compared with our own previous experiences with supervolt therapy during the preceding decade, the early reactions seemed more severe and the incidence of postradiation edema greater than necessary, reminiscent of older experiences with medium volt therapy or earlier supervolt therapy with shorter treatment time. It was therefore decided early in 1958 to increase protraction and to adjust the total dose more individually to the observed response of tumor and mucosa. In the treatment of 21 patients between 1958 and 1960 (Group II), we followed a basic plan which called for a midline dose of 5,000 r in 6 weeks, to be increased—as indicated by the observed response of tumor and mucosa—to 5,500 r in about 7 weeks or 6,000 r in about $7\frac{1}{2}$ weeks. Thus the average protraction in Group I was 40 days for 6,000 r and in Group II 48 days for 5,500 r or 53 days for 6,000 r—about 30 per cent increase in treatment time.

A comparison of these two groups has clearly shown that both subjective and objective morbidity were significantly reduced by the greater protraction. Patients in the second group have supported treatment without any, or with very minimal, discomfort. The laryngologists who observed these patients with us during and following irradiation made spontaneous comments about the "ease with which patients are now going through treatment," instead of the notes previously found in the records, such as "the usual postirradiation edema."

Objectively there was a marked difference in demonstrable reaction (Table I). All 7 patients (Stages I and II) in the first group (1957) developed thick, confluent false membranes between the 19th and 27th treatment day, when the midline doses had reached 3,000 to 4,000 r; these membranes lasted 4 to 6 weeks—several weeks beyond the completion of therapy. In contrast, none of the 9 patients with Stage I carcinoma in the second group (1958–1960) showed a confluent false membrane. In 2, there was a thin, patchy false membrane which had subsided by the end of therapy. Of 12 patients with Stage II carcinoma in the second group, 3 showed a confluent membrane.

With regard to edema, it is important to differentiate between early and late edema.

TABLE I

CARCINOMA OF THE VOCAL CORD
1957–1960

	No. Treated	False Membrane		Edema		Controlled 4/1/62		Uncontrolled
		C[1]	P[2]	Early	Late	Normal Larynx	Poor Larynx	
Stage I								
1957	4	4		2	1	4		
1958–1960	9	0	2	3	—	8		1*
Stage II								
1957	3	3			3		2	1**
1958–1960	12	3		2	1	7		5†
Stages I and II								
1957–1960	28					19	2	7

* Cordectomy 9 months post treatment.
** Died of hemorrhage 29 months post treatment.
† Four laryngectomies; 1 refused laryngectomy.
C[1] = thick, confluent false membrane.
P[2] = patchy, thin false membrane.

mentioned reports, we have felt rather certain for quite some time that epidermoid carcinoma can be controlled as consistently without, or without significant, mucosal reactions if sufficient protraction and radiation in the supervolt range are used.

At the University of California Hospitals, San Francisco, during the last 5 years, we have consistently treated epidermoid carcinomas of the upper respiratory and alimentary mucous membranes with supervolt irradiation (1 mev. and cobalt 60 teletherapy), and with a protraction of not less than 6 weeks and frequently of 8 to 10 without exceeding tumor doses of 6,000 r or occasionally 6,500 r. Concluding from our experiences with 800 kv. irradiation, we had stated in 1950:[2] "A dose in the range of 5,000 to 6,000 r is sufficient to control most neoplasms which can be sterilized by ionizing radiation, and some require considerably less . . . an increase in dose will not control a tumor which is incurable either by virtue of its essential biologic unsuitability for radiation therapy or its anatomic environment in tissues which profoundly alter its radiobiologic properties." Additional experience has reconfirmed this conclusion. Occasional desperate attempts to accomplish the impossible by forcing the dose have almost always lead to increased tissue damage without sufficient improvement of tumor effect to justify the added morbidity and risk. Specifically in the treatment of carcinoma of the larynx, we are now convinced that an increase of dose beyond 6,000 r, or at the most 6,500 r (even with protraction over 8 to 10 weeks), leads to a point of diminishing returns. The late changes, then, are such as to make evaluation of tumor control more difficult and unsatisfactory, and in some instances have left the larynx in a condition such that laryngectomy would have been preferable, even if the tumor seemed to have been controlled. Neither do we believe that longer protraction necessitates as great an increase in the total dose as is frequently assumed, although we will make some allowance for this. Likewise, it has now been satisfactorily demonstrated[4] that the influence of reduced radiobiologic effectiveness with the use of supervolt irradiation has been greatly overemphasized by some.

There is still a rather prevalent opinion, however, even among some of the most experienced radiotherapists, that formation of a false membrane is necessary for the control of epidermoid carcinoma and that with less aggressive treatment the sterilization of the tumor may be less certain and results may become inferior. We therefore offer this preliminary report of our observations on treatment of carcinoma of the vocal cords, representing part of a more systematic study of the effect of ultraprotracted supervolt therapy on epidermoid carcinoma of the larynx, pharynx, and oral mucosa. In spite of the relatively short observation time and the small number of patients, we believe that certain conclusions are already permissible, since the observed changes are remarkably uniform and consistent with previous observations by ourselves and others.

We include in this analysis only those patients whose entire treatment and follow-up were personally supervised and recorded by one or both of the authors (Table 1): 28 patients with carcinoma of the vocal cord (13 Stage I and 15 Stage II) were treated between January, 1957, when one of the authors first became associated with this department, and December, 1960, using 1 mev. radiation (half value layer 3.2 mm. Pb) with opposing parallel fields of 5×5 or 6×6 cm. The dose was calculated at the midline between the center of the two lateral fields, as measured by caliper in each patient.

In the treatment of the 7 patients treated in 1957 (Group I), the technique that had been consistently used in this department since the installation in 1955 of the presently operating 1 mev. equipment was not altered, so that we might familiarize ourselves with the details of its effect on tumor and tissues: 6,000 r midline dose in 6 weeks, without significant individual variations. The cure rate with this technique had been

moderate radiosensitivity cannot be sterilized without the associated mucosal reaction—an epithelitis with formation of a "good" confluent false membrane. Thus a false membrane was not only considered to be unavoidable, but desirable, and the time for the appearance of such reaction and its intensity were used as clinical guides to determine the dose tolerated by the individual patient and necessary for the sterilization of the particular tumor. Accumulated experience over the last two decades has demonstrated that this applies only to certain radiotherapeutic techniques: with the use of medium volt radiation and/or limited protraction of treatment time (3 to 4 weeks), epidermoid carcinomas indeed cannot be sterilized without significant membranous mucositis.

On the other hand, according to "classic" teaching, it was assumed that, with a protraction beyond 4 weeks, an epidermoid carcinoma would become refractory ("radio-immune") and the cure rate would decrease. There now exists ample evidence that protraction beyond 4 weeks, and even beyond 6 weeks, does not jeopardize the effect on epidermoid carcinoma, but that—other factors (quality, dose) remaining equal—such protraction significantly reduces the degree of early mucosal reaction, skin reaction, and late sequelae due to injury of the vasculo-connective tissue. Baclesse's[1] analysis of close to 2,000 cases of epidermoid carcinomas treated by *medium volt therapy* between 1919 and 1950 has shown the value of "ultra-fractionation." In carcinoma of the larynx, the group treated with a protraction of 6 to 8 weeks showed the best 5 year results. Baclesse emphasizes the better condition of the tissues with such protraction, even in the medium volt range.

Previous experiences with 800 kv. and 2 mev. irradiation had taught us that, even with the then more conventional protraction of about 4 weeks, mucosal reactions were less predictable in occurrence and, if they did occur, of less intensity than with comparable doses and protraction of medium volt irradiation and that *in many instances tumor sterilization was accomplished without, or with minimal, mucositis.* The better tissue tolerance of radiation in the supervolt range is now accepted as a fact of unequivocal clinical observation, even if it is not fully explained physically: "The radiation is kinder to the tissues" (Lederman).

Obviously, it could then be expected that a combination of greater protraction with the use of supervoltage radiation would reduce still further the intensity of early reaction and the associated risks of objectionable tissue changes. In his series of 559 glottic carcinomas treated between 1933 and 1959, Lederman[5] has consistently used telecurie therapy in the treatment of all early laryngeal cancers, with a tissue dose of 5,500 to 8,000 r in 6 to 8 weeks. He has reported 5 year cure rates of 81 per cent in Stage I and 61 per cent in Stage II. Early reactions were minimal and late complications very rare. "In our experience," states Lederman,[5] "extending treatment over a *minimum** period of six weeks results in a comfortable patient and generally the patient who does not suffer during treatment rarely encounters complications after treatment. *It should be emphasized that in no circumstances should a brisk or severe local radiation reaction be callously regarded by the radiotherapist as the 'price' the patient has to pay for possible cure** . . . in this series of cases, the incidence of post-radiation complications has been very small. Tracheotomy for radiation oedema during treatment is almost unknown and if it does occur it is nearly always regarded as being the fault of the radiotherapist. Post-radiation tracheotomy, with very rare exceptions, has been due to failure to control the disease."

From our own previous, rather extensive, but unsystematic observations of the effects of supervolt irradiation with different doses and different fractionations used during the last 20 years,[2] and supported by the afore-

* Italics ours.

RADIATION THERAPY OF CARCINOMA OF THE VOCAL CORD WITHOUT MUCOSAL REACTION*

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IN THE treatment of early carcinoma of the vocal cord which does not extend to the anterior commissure or arytenoid mucosa (Stage I), the choice between cordectomy and radiation therapy has been optional when equally competent services were available. A cure rate of at least 80 per cent is consistently obtained by either procedure. In Stage II, with extension into the anterior commissure or posteriorly but without fixation, the choice lies between a primary laryngectomy or radiation therapy with laryngectomy reserved for radiation failure. The results measured by 5 year cure rate, again, are the same (50 per cent[3] to 60 per cent[5]), but in only 1 out of 5 survivors is it necessary to resort to laryngectomy, while 4 retain the larynx if radiation therapy is used initially.

Formerly, the disadvantages to radiation therapy were the early morbidity associated with the mucosal reaction, which was often greater than the surgical morbidity, the corresponding late manifestations of radiation damage, such as edema, chondritis, cartilaginous necrosis, and the permanently greater vulnerability of the heavily irradiated mucosa.

The early mucosal reaction—mucositis or epithelitis with formation of a confluent false membrane—which occurs during or immediately following radiation therapy results from the destruction of the epithelial covering. This reaction, in itself, is not objectionable. It heals with regeneration of the epithelium. It is, however, an indication that the mucous membrane has been irradiated beyond the point of complete biologic recovery. Even in instances in which gross pathologic changes, such as persistent late edema, marked telangiectasia, atrophy, or ulceration, do not occur and despite the grossly normal appearance of the mucosa and normal laryngeal function, a mucosa that has passed through the stage of a coherent false membrane remains less resistant to otherwise inconsequential injuries, such as minor infections and irritations.

Late reactions are caused by injury to the vasculo-connective tissue and manifest themselves months or years after therapy. They occur very rarely in patients who have not shown marked early reaction. This is a general radiobiologic observation. In the treatment of pelvic carcinomas, for instance, late radiation changes of clinical significance (injury of rectum or bladder, or pelvic fibrosis) are rarities, if they occur at all, in patients who did not have significant symptoms of intestinal mucosal reaction during the course of therapy. Nature has thus provided us with an effective warning system: the dose necessary to cause significant late vasculo-connective tissue damage of clinical importance is higher than that necessary to cause early reactions of the mucosal surfaces. If signs and symptoms of early mucosal changes are heeded and treatment adjusted accordingly, objectionable late changes can almost certainly be avoided. This is the reason for the necessity for close observation of a patient under treatment and for flexibility of any preconceived treatment plan.

Can early mucosal changes be avoided without jeopardizing the effect on the tumor?

During the first decades of radiation therapy, based mainly on Coutard's fundamental clinical observations, there grew up an adage that epidermoid carcinomas of

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extending inferiorly may offer similar difficulties.

The roentgen diagnosis of involvement of the anterior commissure is more easily made by clinical means (laryngoscopy) than by laryngography. When there is contrast filling of the anterior aspect between the cords, displacement is definite roentgen evidence of disease.

By contrast examination infraglottic tumors and/or extensions can be easily diagnosed. Only one error was made in the evaluation of infraglottic extension and in this patient the amount of tumor extension was minimal.

The roentgen appearance of anterior infraglottic tumor is characteristic. When there is fixation of the cord, there is fullness in the infraglottic space; however, this roentgen appearance usually can be distinguished from infraglottic tumor.

SUMMARY

Study of 32 cases of transglottic, 24 cases of infraglottic, and 15 cases of glottic tumors has revealed characteristic roentgen features. These have been correlated with the pathologic findings of the gross specimen.

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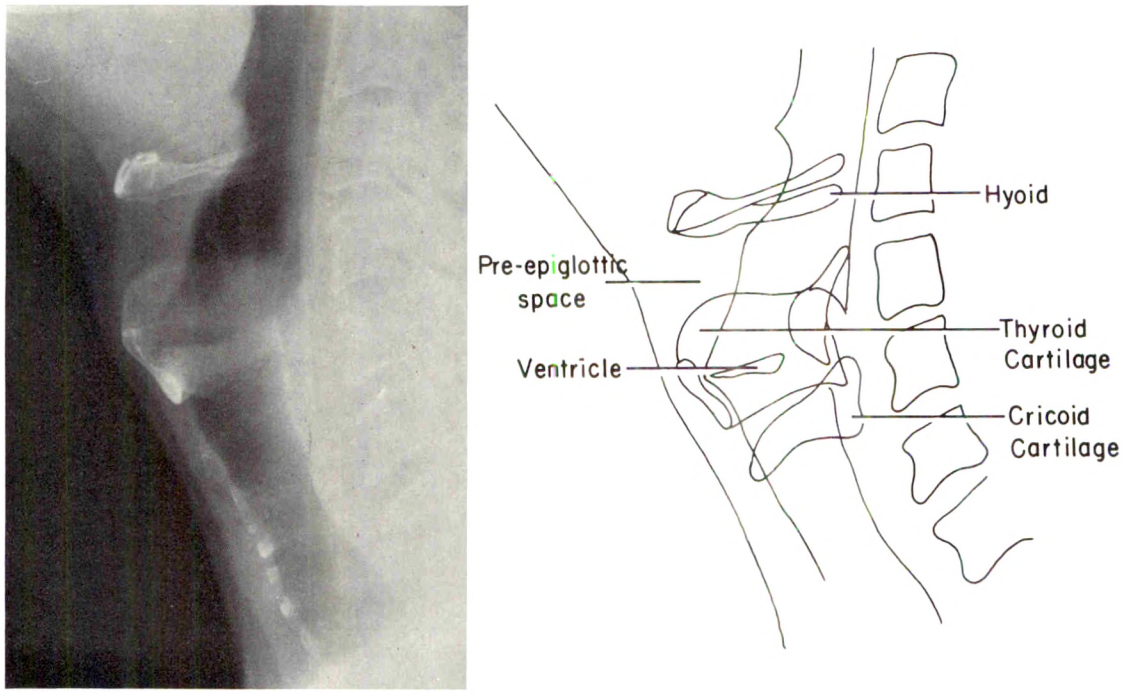


Fig. 14. Lateral view of the neck. Soft tissue technique. This view is taken so as to examine the laryngeal cartilages and the pre-epiglottic space.

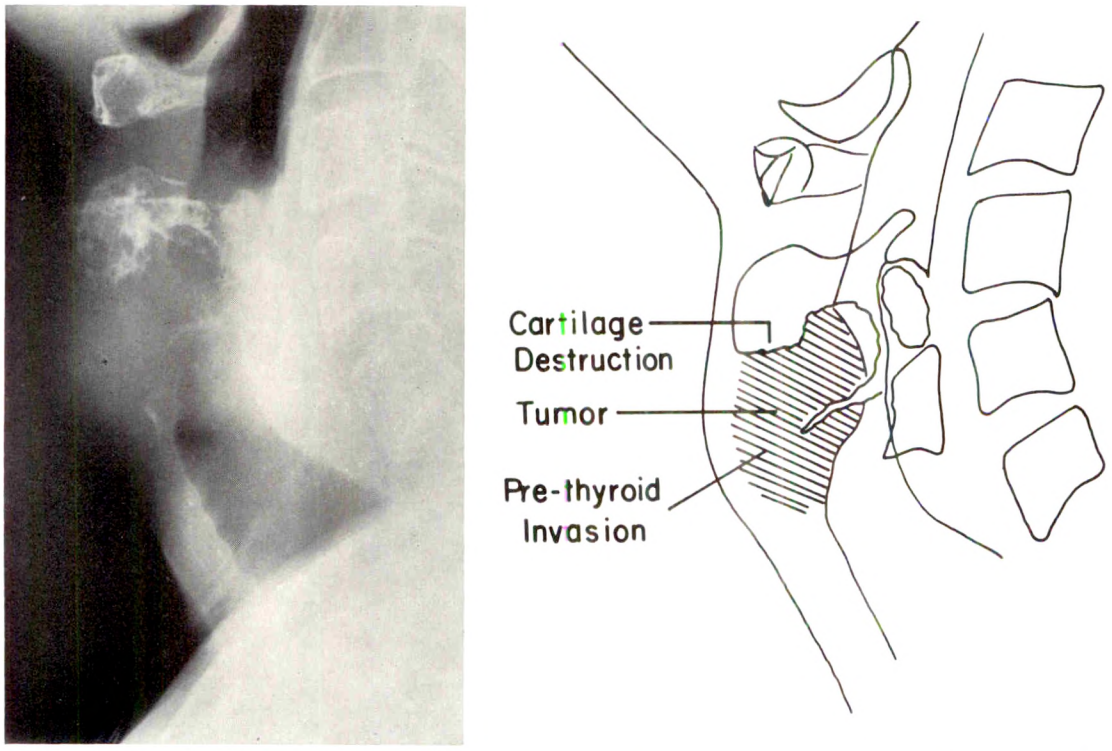


Fig. 15. Lateral view of the neck. Soft tissue technique. There is a large cancer of the larynx which has destroyed the thyroid cartilage and bulges anteriorly into the soft tissues.

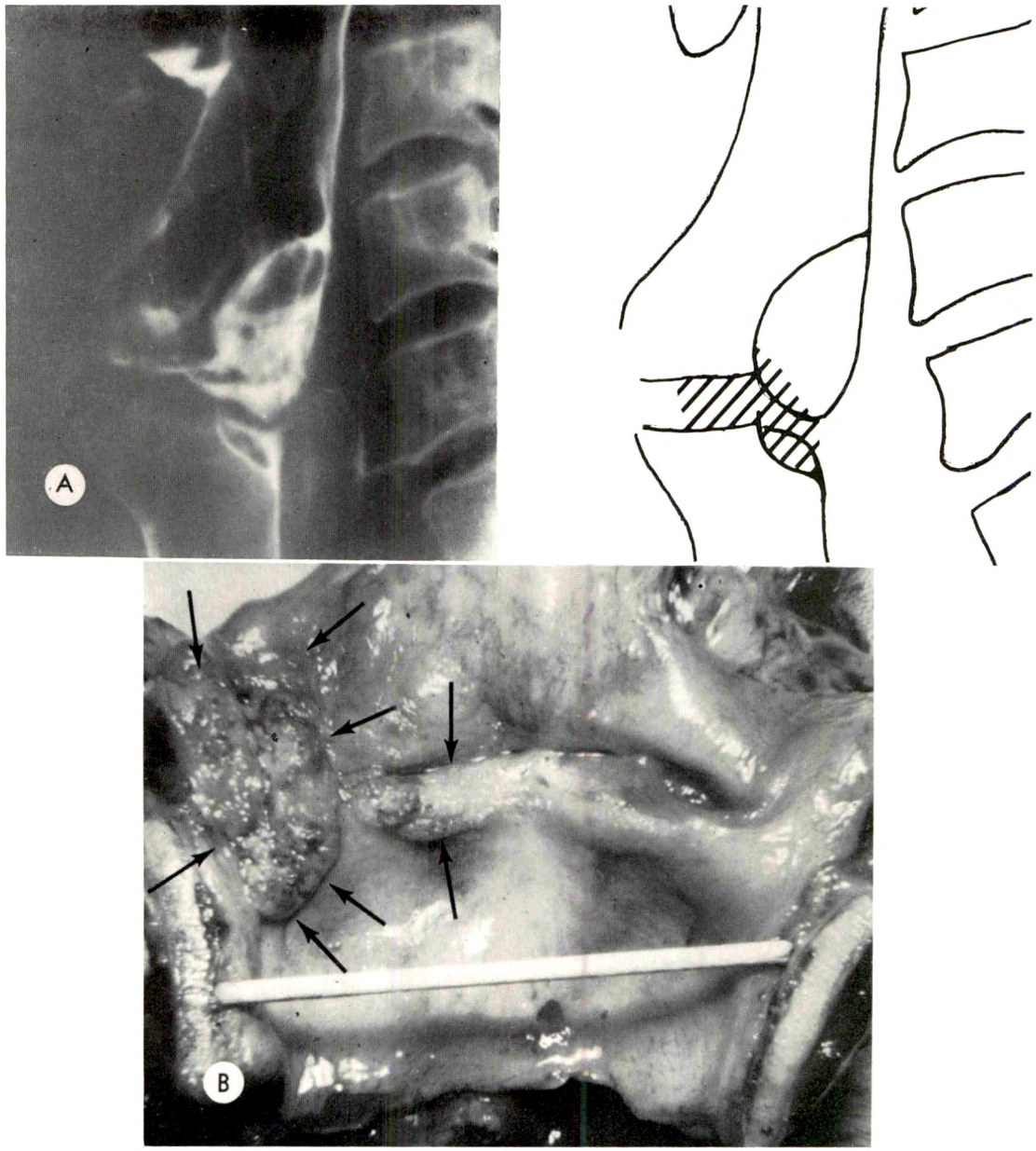


FIG. 13. Glottic cancer with arytenoid extension. (*A*) Lateral view. There is a posterior subglottic mass. This represents tumor extending from a known glottic lesion onto the posterior commissure and arytenoid. (*B*) Laryngectomy specimen shows the tumor mass occupying the true cord and a larger mass extending posteriorly onto the mucosa overlying the arytenoid.

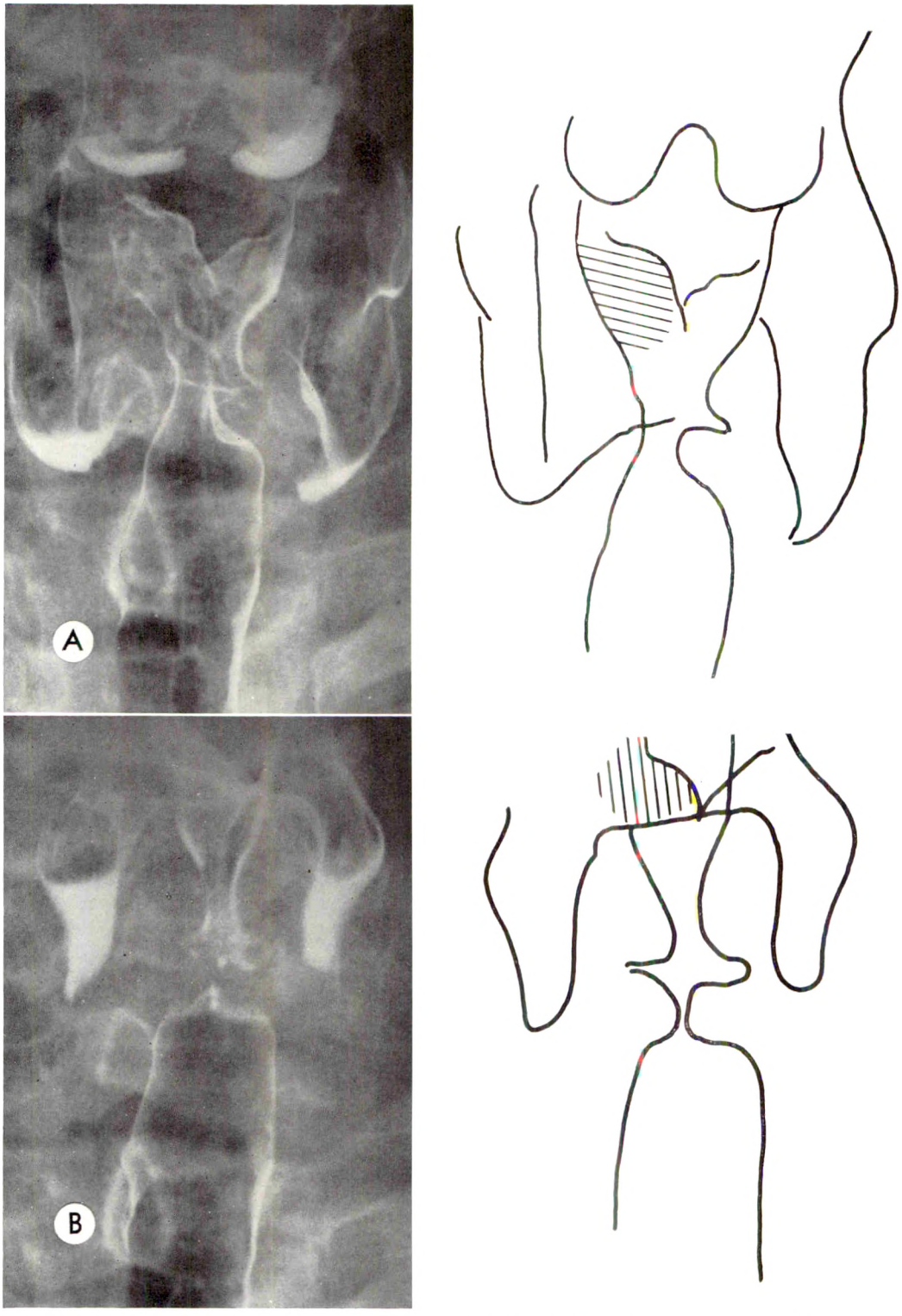
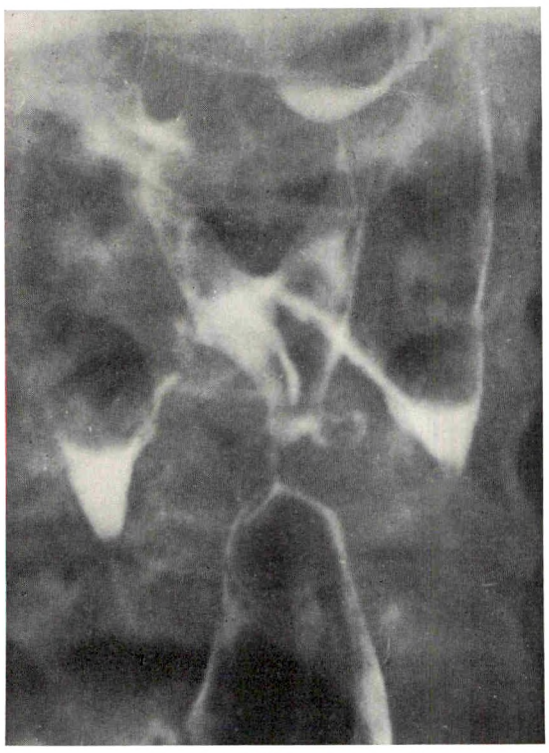


Fig. 12. Carcinoma of the mucosa over the arytenoid. (*A*) *Modified Valsalva maneuver.* The right arytenoid is irregularly enlarged. (*B*) *Phonation.* The cords are normal and mobile. The patient is living without evidence of tumor 6 years following radiation therapy.



FIG. 10. (*C*) The operative specimen confirms the roentgen image.



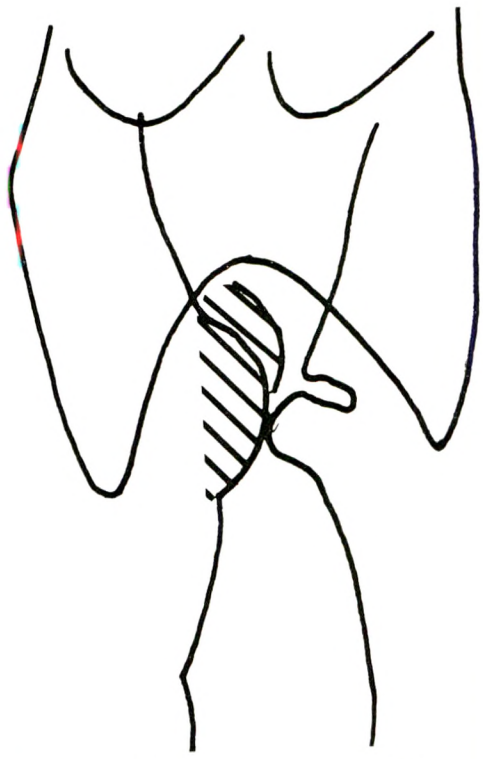


FIG. 11. Small transglottic cancer. *Phonation*. There is a tumor mass involving the right true and false cords and obliterating the ventricle. Since the tumor crosses the ventricle, it is classified as transglottic.

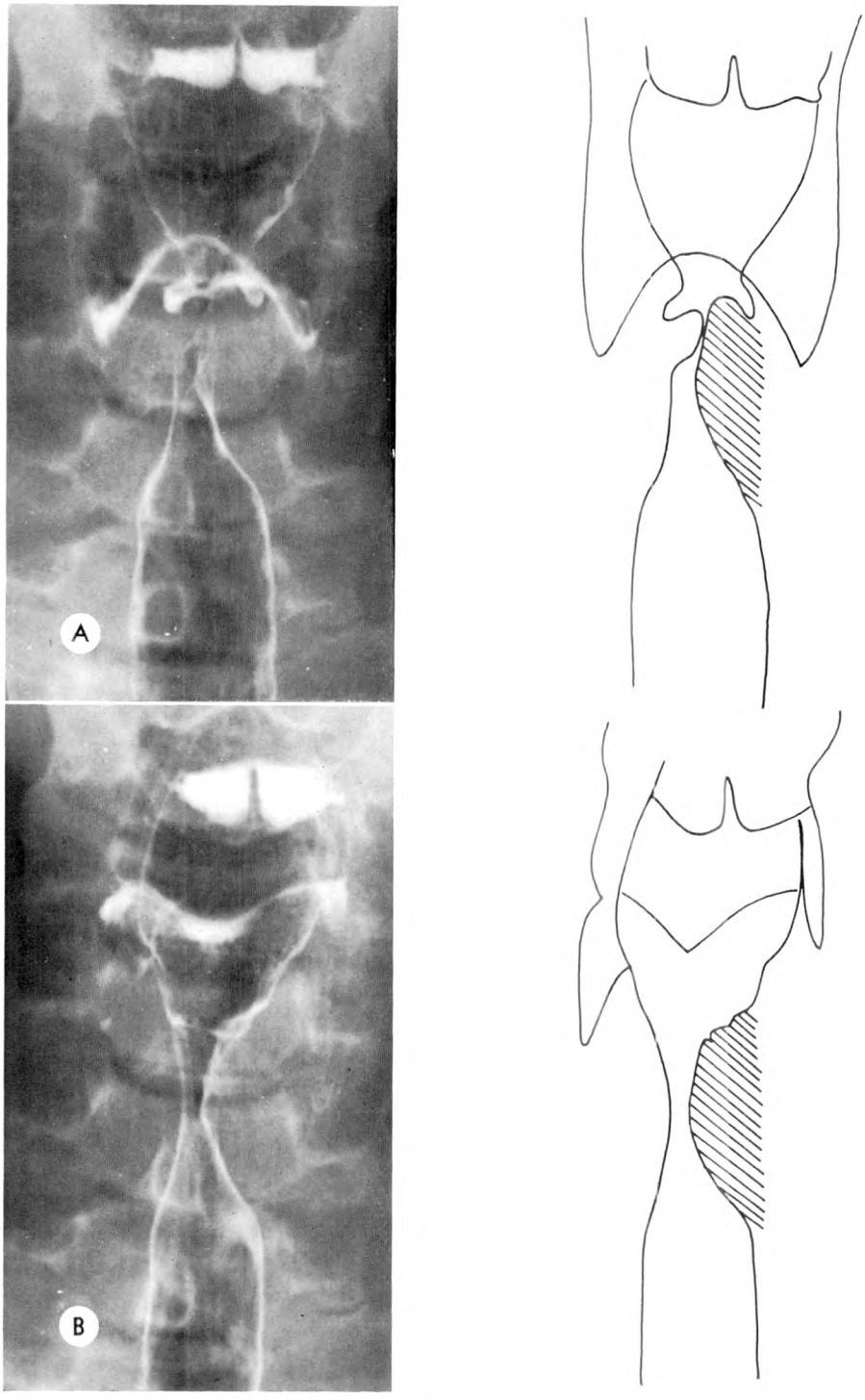


Fig. 10. Carcinoma of the left true cord, with fixation and large subglottic extension. A comparison of roentgenograms during (*A*) *phonation* and (*B*) *inspiration* shows lack of mobility of the enlarged left cord. There is a smoothly outlined subglottic mass which is bowed medially. The configuration of this subglottic mass does not change from inspiration to phonation, another indication that this represents tumor.

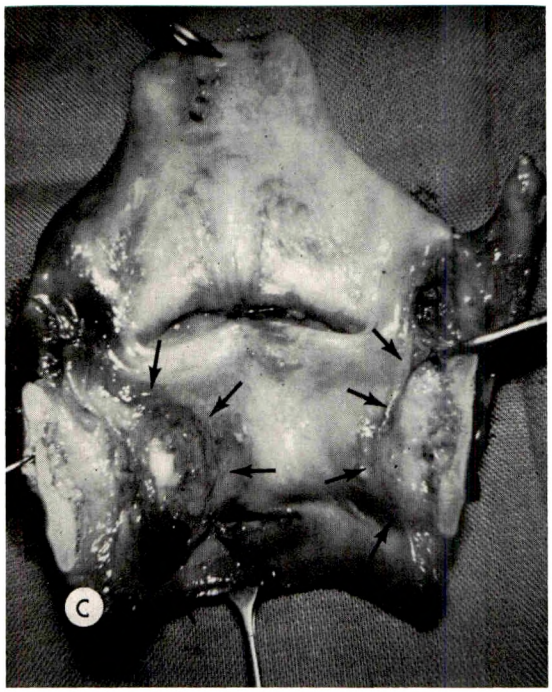


FIG. 9. (*C*) Laryngectomy specimen was opened posteriorly, cutting through the tumor which occupied and infiltrated the posterior laryngeal wall. It therefore extends to the right and left of the incision in the specimen as indicated by the arrows.

D. ARYTENOID TUMORS

Occasionally, tumors involve the arytenoid. Primary neoplasm of the arytenoid must be quite rare as we have only seen 2 such cases (Fig. 12, *A* and *B*). However, glottic tumors may extend to the arytenoid (Fig. 13, *A* and *B*). While this is quite unusual, it must always be considered when there is fixation of the true cord, or when there is enlargement of one of the arytenoids. Unfortunately, the arytenoids reflect changes within the larynx and often one or both are enlarged following biopsy or radiation therapy, or even when associated with a remote laryngeal lesion. Under these circumstances the laryngogram demonstrates the arytenoid to be enlarged, smooth in outline and frequently the cord is mobile. Surgical pathologic examination has demonstrated only edema in such cases. When tumors involve the arytenoid, the laryngogram demonstrates enlargement which may be smooth in outline, although more often it is lobular in contour. In glottic tumors, when the posterior aspect of the glottis is involved and there is roentgen evidence of what appears to be posterior infraglottic tumor, extension onto the arytenoid is probable.

E. CARTILAGE DESTRUCTION

The laryngographic technique employed makes it impossible to evaluate the laryngeal cartilages and, because of this, special roentgenograms for soft tissue detail are taken prior to the contrast examination (Fig. 14 and 15).

F. BENIGN VERSUS MALIGNANT DISEASE

Laryngography is not meant to be a screening examination but rather a technique to be used in association with laryngoscopy and biopsy. Laryngography should be performed prior to biopsy since any operative procedure produces edema and distortion of the laryngeal structures. While chronic inflammatory disease produces some changes with rather characteristic features, the differentiation between benign and malignant neoplasms solely by laryngography is impossible (Fig. 3).

CAUSE OF ROENTGEN ERRORS

In the classification of laryngeal tumors, and in discerning the size and extent of tumor involvement, as well as the interference of function, contrast roentgen study has proved to be accurate. The only significant number of errors in the past was made because of inadequate evaluation of the ventricle. Large, bulky glottic and infraglottic tumors may displace the ventricle upward and make it appear as though the ventricle failed to fill with contrast substance (Fig. 7, *A* and *B*). A reevaluation of the roentgenograms of these cases (4 of the 24 cases) showed that the error was not one of technique but of misinterpretation.

Large tumors also may almost obliterate the ventricle, making careful roentgen technique imperative. Supraglottic tumors

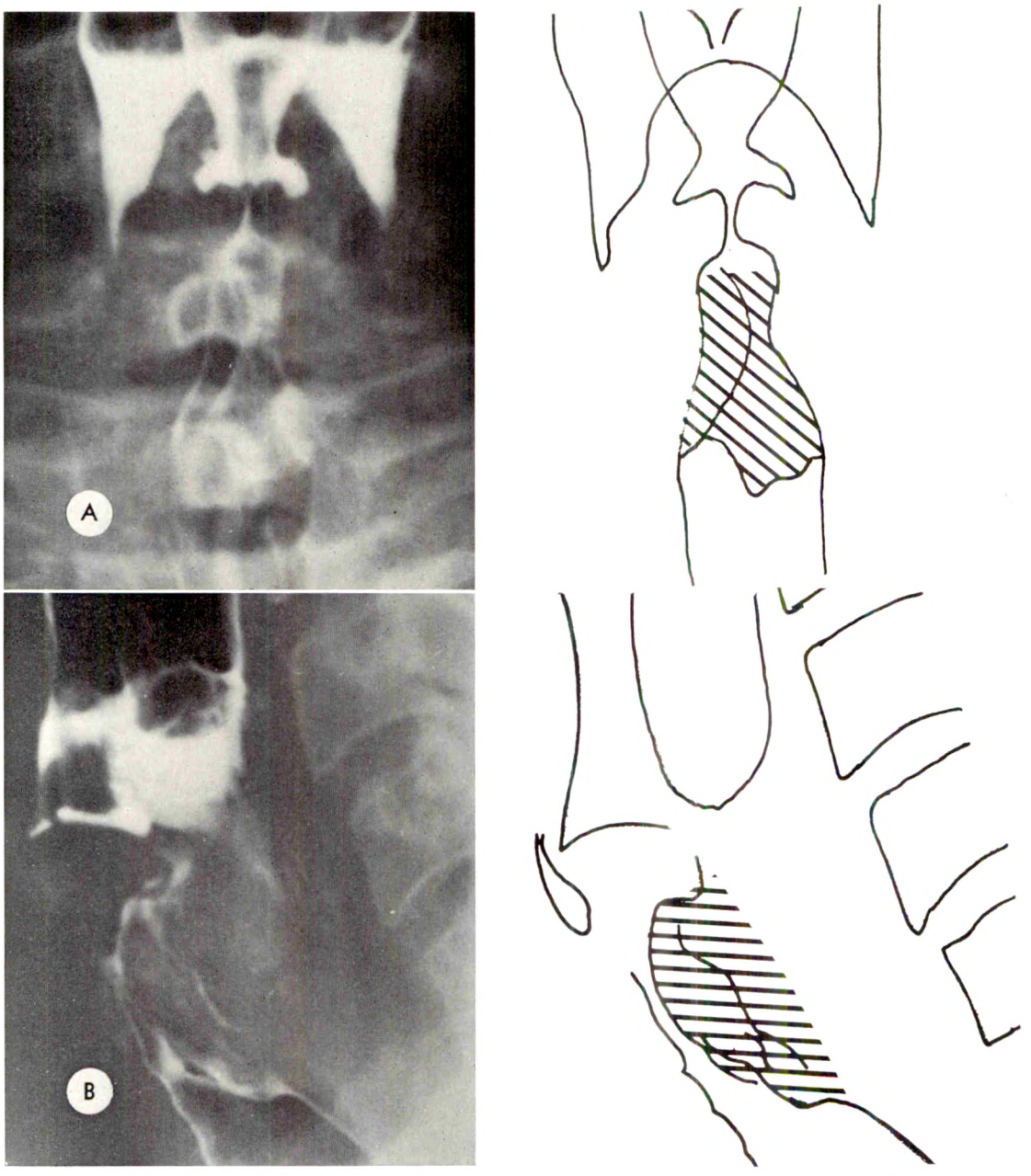


Fig. 9. Primary carcinoma of the infraglottic space without glottic involvement. (*A*) Frontal view. The true cords and immediate subglottic area appear normal. Below the cords there is a large fungating tumor. (*B*) Lateral view. The large tumor mass arising from the posterior wall of the larynx is completely outlined with contrast substance. The limits of the tumor are clearly defined.

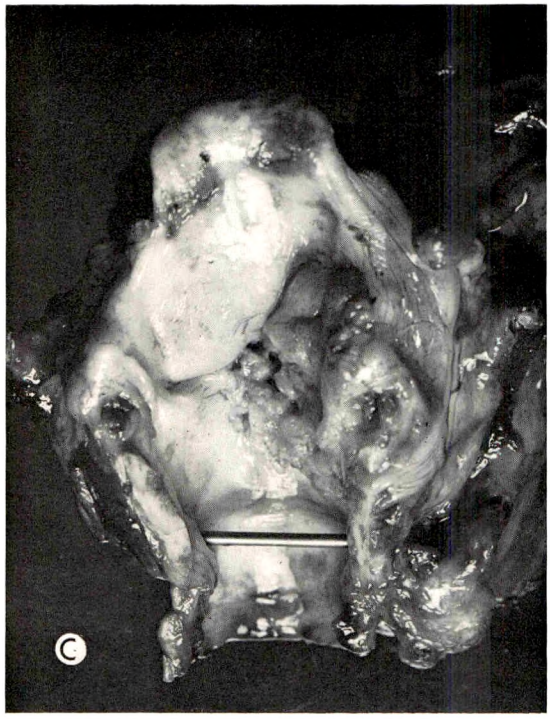


FIG. 8. (*C*) Laryngectomy specimen, opened posteriorly, shows the tumor conforming exactly to the roentgen image. (Reproduced by permission of *Laryngoscope*.)

irregular in outline or smooth as though the tumor has extended submucosally, leaving the surface intact. It is of importance, of course, to visualize adequately the inferior extent of the true cords and this is readily done on roentgenograms in the frontal projection taken during phonation and the Valsalva maneuvers. Roentgenograms taken at the time of these maneuvers demonstrate that normally the infraglottic area immediately below the level of the cords makes a sharp right angle with the cords. Any change in the size of the immediate infraglottic area and any failure or deviation from the sharp right angle that the cords and infraglottic area make denote a lesion at that site. The infraglottic component may be present either laterally, anteriorly or in combination. Anterior infraglottic extension presents a characteristic roentgen image with a scalloped margin replacing the normal straight smooth line that represents the anterior border of the larynx (Fig. 7 *B*; and 8 *B*).

When the glottic tumor has involved the intrinsic muscles and the cord becomes fixed, laryngograms in the frontal projection demonstrate an obtuse angle between the cord and the trachea. This contour cannot be visualized in the lateral projection. However, it must be differentiated from a lateral infraglottic extension. Ordinarily, with a cord fixed by tumor, the area between the cord and the larynx changes from an ordinary right angle to a gentle obtuse curvature. The curvature is usually concave to the midline and extends for only a short distance below the cord (Fig. 2, *A* and *B*). A tumor within the infraglottic space, however, extends for a considerable distance below the cord and the mass is convex to the midline (Fig. 7 *A*; 8 *A*; and 10 *A*). Roentgen evidence of anterior infraglottic extension is usually present.

C. TRANSGLOTTIC TUMORS

When tumor involves both sides of the ventricle, the lesion is classified as transglottic (Fig. 8, *A–C*, and 11). This type of tumor carries the worst prognosis of all laryngeal cancers. Tumors of the true cord may extend craniad crossing the ventricle to involve the supraglottic structures and become transglottic. Transglottic tumors may originate in the supraglottic structures and extend downward making it impossible to perform "conservation of function" surgical procedures. Reference to this type of extension will be made in a subsequent publication. Since the ventricle has been crossed by tumor, obliteration of the ventricle should be, and indeed is, the most reliable sign of transglottic tumor (Fig. 8, *A* and *B*; and 11). Growth limited to the true cord can attain a large size and may, by its bulk, displace or seemingly obliterate the ventricle. These changes may then be incorrectly assessed as transglottic tumor (Fig. 7, *A* and *B*). In our experience there were no false negatives—never was there a normal ventricle with a transglottic tumor.

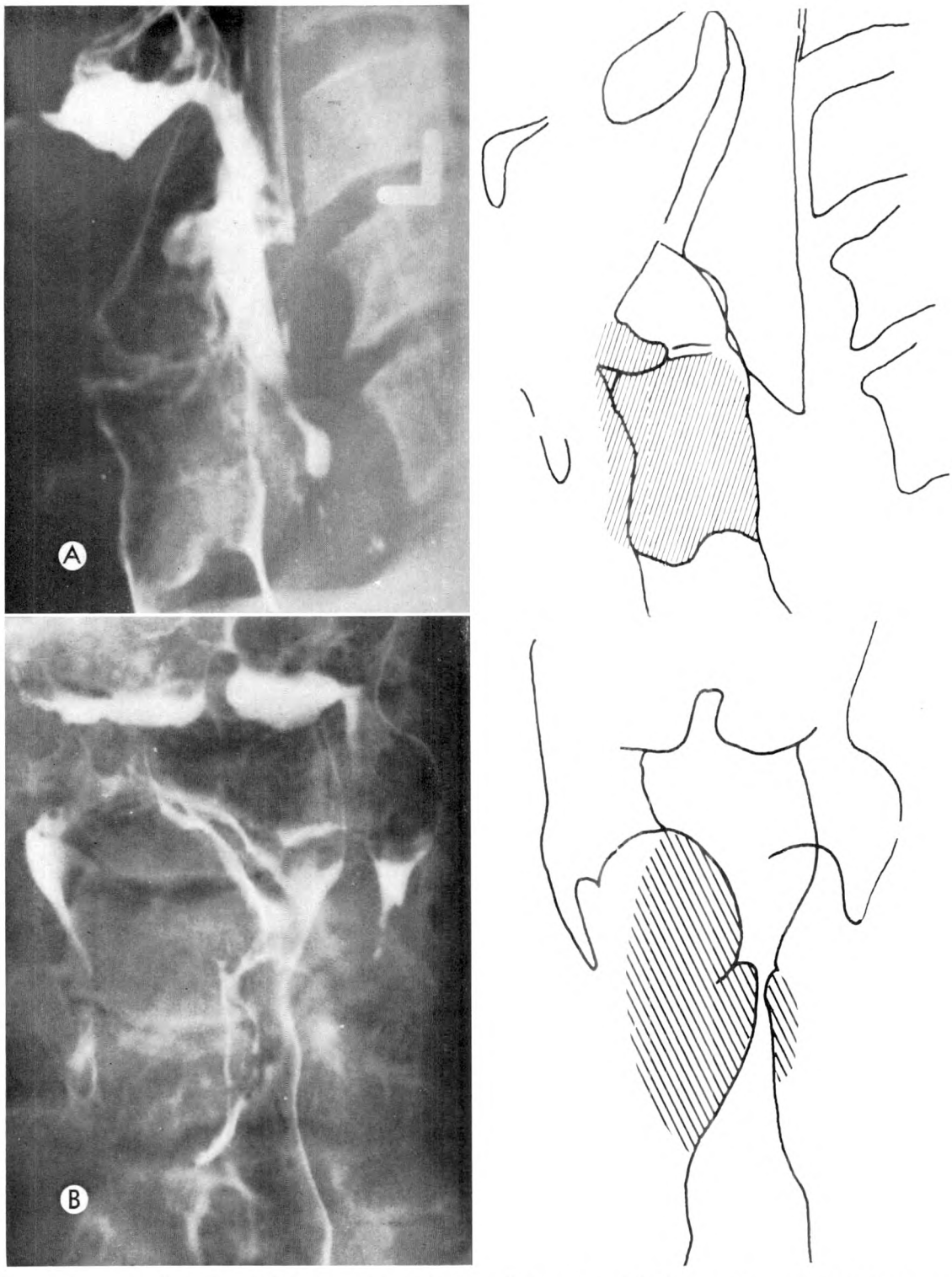


Fig. 8. Transglottic tumor (*A*) Lateral view. (*B*) Frontal view. The right laryngeal ventricle is obliterated by tumor which extends from above the false cord to a point 2 cm. into the subglottic area. The cord is fixed.

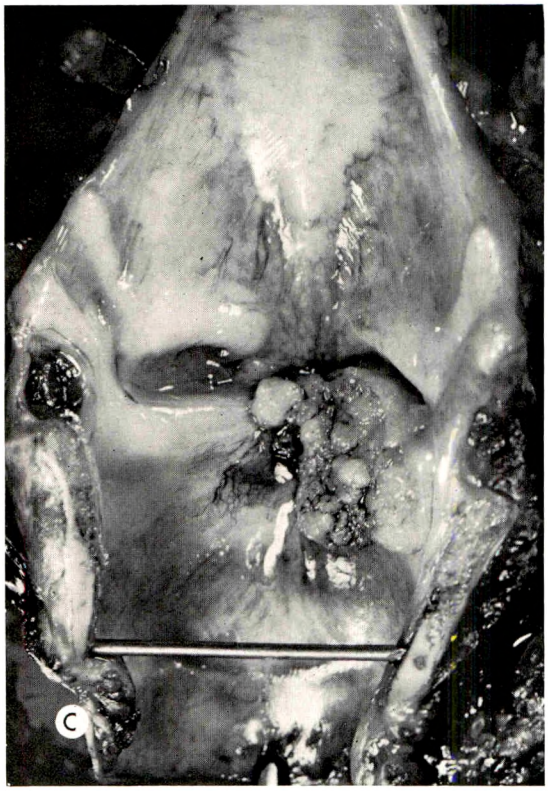


FIG. 7. (*C*) Laryngectomy specimen shows the tumor mass confined to the true cord, anterior commissure and infraglottic area. The location and bulk of the tumor distorts the ventricle, which could make its recognition difficult. (Reproduced by permission of *Laryngoscope*.)

picture of a polypoid mass, the neoplasm may be benign as well as malignant.

2. *Mobility*. A comparison of the roentgenograms in inspirtion and phonation readily demonstrates the motion of the cords. Lack of motion of the cord implies involvement of the intrinsic muscles of the larynx (Fig. 2, *A* and *B*). If the tumor is large and bulky it may appear as though there is a fixed, motionless cord at the time of laryngoscopy. Laryngograms more accurately demonstrate motion than indirect laryngoscopy. The roentgen features of a fixed cord are easily distinguished from those of a paretic cord (Fig. 6, *A* and *B*).

3. *Anterior Commissure*. On the lateral laryngogram the contrast substance extends downward from the base of the epiglottis past the ventricles to reach the subglottic region. This contrast outline represents the anterior aspect of the midline of the epiglottis, anterior commissure and the midline of the larynx, and is separated from the thyroid cartilage by a thickness of tissue less than 0.2 cm. A consistent increase in this thickness denotes anterior commissure involvement. Failure to fill this area at the level of the true cords with contrast substance suggests involvement of the anterior commissure (Fig. 1, *A–C*; 7, *A–C*; and 8, *A–C*).

B. INFRAGLOTTIC TUMORS

While neoplasms may rarely originate in the infraglottic space, infraglottic extension of glottic cancer is the more common origin of these tumors. If the primary infraglottic tumor extends upward to involve the glottis, it is impossible to distinguish pathologically or roentgenographically from the more common glottic tumor that has extended downward. Tumor involvement of the infraglottic space, whether there is involvement of the glottis or not and regardless of the exact site of its origin, is classified as an infraglottic tumor. When the tumor is present only in the infraglottic area, it presents a roentgen picture of a mass either smooth or irregular in outline and attached to the wall of the larynx (Fig. 9, *A–C*). At times, a great deal of effort is necessary to demonstrate the superior and inferior limits of the tumor. We have found that by having the patient cough gently the contrast material more adequately coats portions of the infraglottic area after other attempts have failed. Normally, the larynx and the bottom of the true cords meet, forming a sharp, right angle. This is best seen on the roentgenograms taken during phonation and the Valsalva maneuver in which the glottis is closed. When the tumor involves the glottis and the infraglottic area, this angle becomes obtuse and may even bow into the lumen of the larynx (Fig. 10, *A–C*). The subglottic mass may be

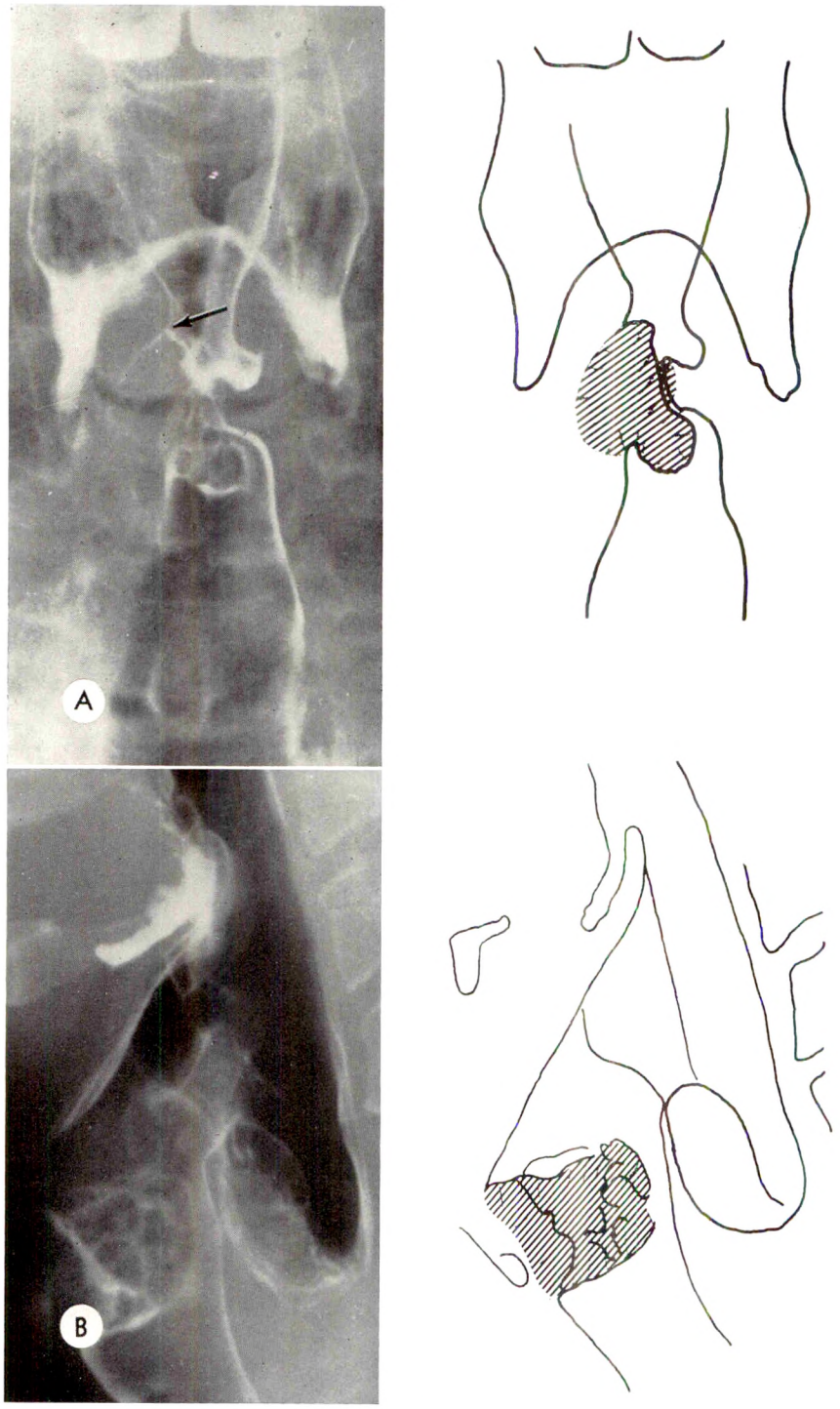


Fig. 7. Glottic cancer with infraglottic extension. (*A*) *Phonation.* Frontal view. A rounded polypoid lesion occupies the entire right true cord and extends into the adjacent infraglottic area. The corresponding ventricle is represented by a thin line of contrast substance elevated and compressed by the tumor (arrow). Preservation of the ventricle in spite of distortion indicates that the tumor has not crossed the ventricle. (*B*) Lateral view. There is anterior infraglottic extension with separation of the contrast substance from the thyroid cartilage. Contrast substance also coats the lateral infraglottic extension.

enough to obscure the ventricle and the subglottic area, making evaluation of these areas by clinical means impossible. It appears on the roentgenograms as a mass usually smooth in outline, best seen with the cord retracted in inspiration. In this maneuver the anterior ends of the ventricles approximate at the midline, while the posterior portions are displaced laterally by the upward and outward movement of the cords (Fig. 5). Thus the anterior posterior position of the mass can be determined.

At times, even though the mass is pedunculated, it may be as large as the cord itself and may appear to project above the ventricle or into the infraglottic space. Preservation of these structures outlined with contrast material, seen projected through the tumor mass, will quickly establish its pedunculated character (Fig. 4, *A* and *B*). While neoplasms may present a

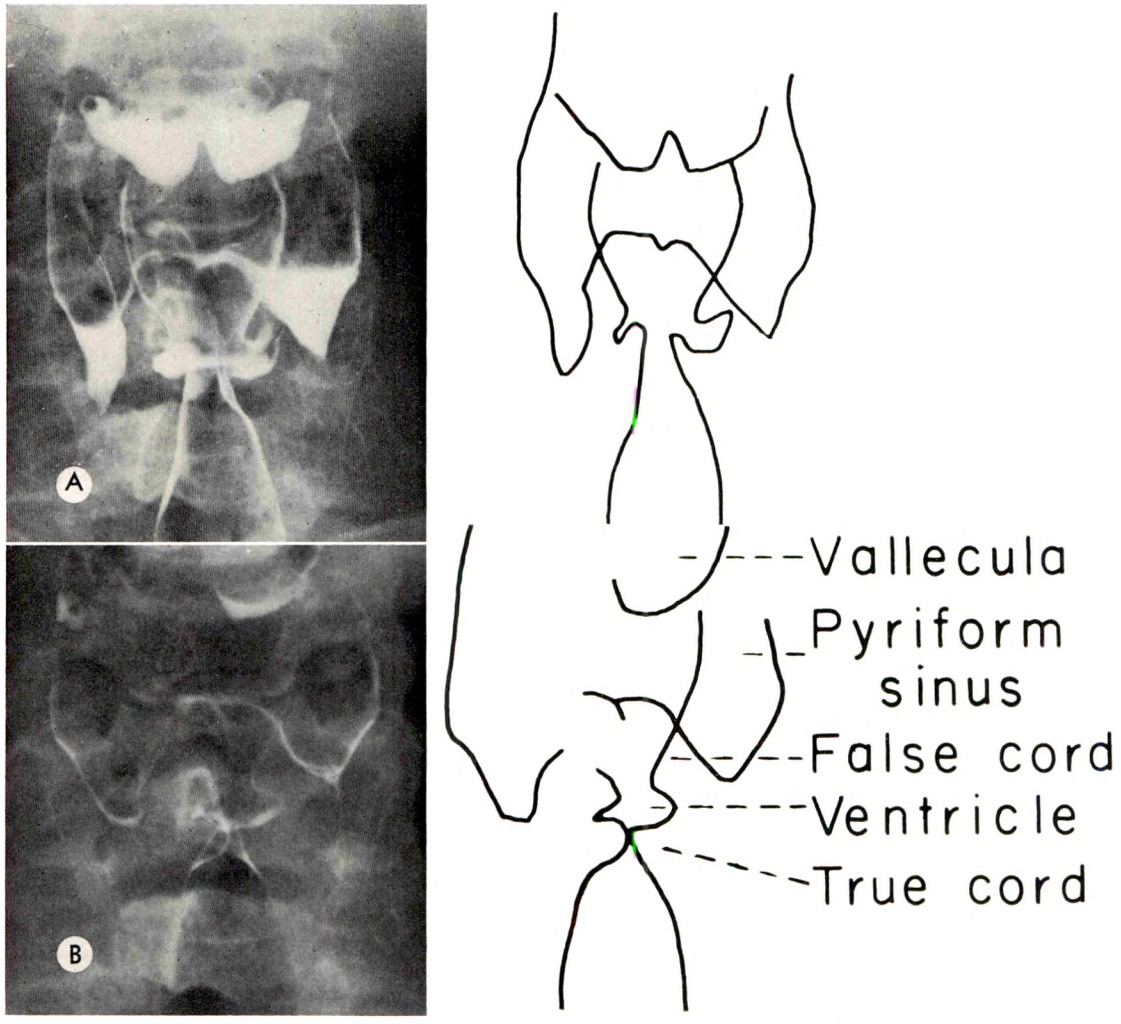


FIG. 6. Laryngeal palsy. (*A*) *Inspiration.* The right true cord retracts normally. The free edge of the left true cord appears thinner than normal, and remains in the midline. The ventricle on this side is enlarged. The infraglottic area is fuller than normal, although not convex toward the midline. (*B*) *Phonation.* During this phase the cords oppose, the ventricle on the affected side is dilated and the true cord is thinned. Instead of the normal infraglottic angle, there is fullness of the subglottic space, which is concave toward the midline. (Reproduced by permission of *Radiology*.)

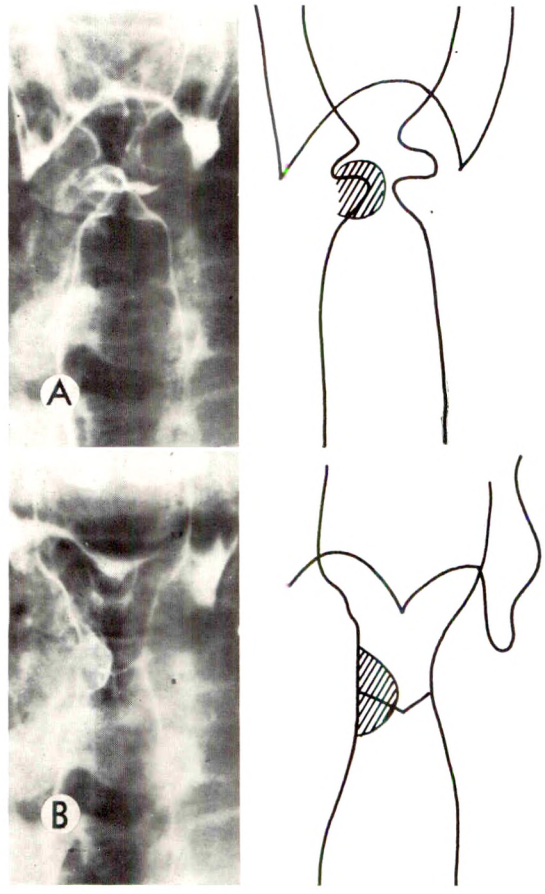


Fig. 4. Polypoid carcinoma of the right true cord. (*A*) *Phonation.* Frontal view. The cords oppose normally. There is a polypoid mass involving the right true cord. The normal anterior portion of the true cord is seen through this mass, indicating a posterior position of the tumor. There is preservation of the ventricle and supraglotic structures. (*B*) *Inspiration.* Frontal view. The cords retract normally. Although the bulky tumor projects above the level of the ventricle, the ventricle is intact. This patient is free from tumor 2 years after radiation therapy.

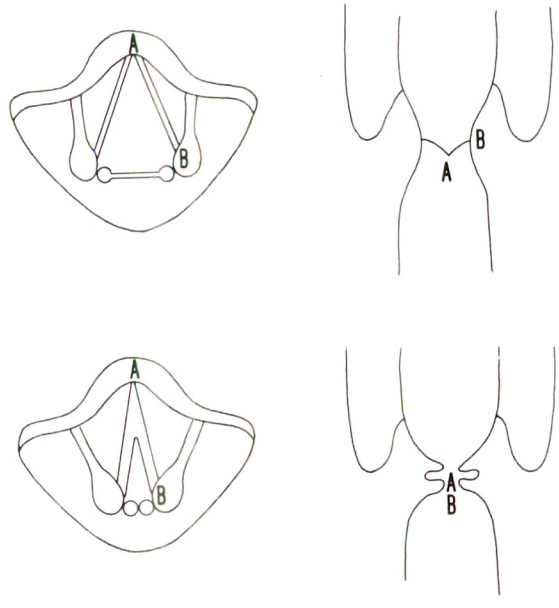
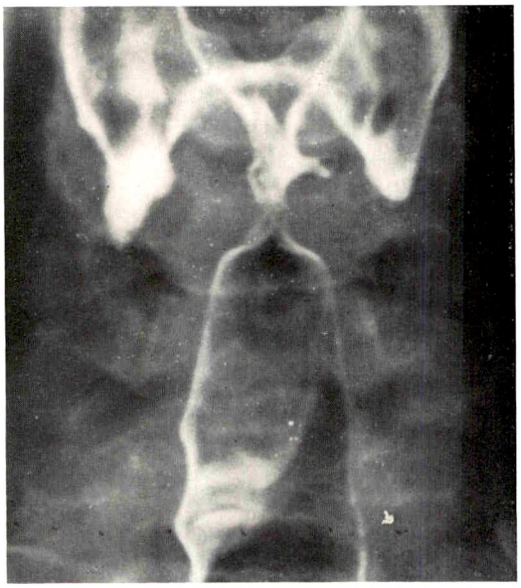


Fig. 5. Line drawings illustrating retraction of the cords in inspiration. In this maneuver the anterior ends of the ventricles approximate at the midline, while the posterior portion is displaced laterally by the upward and outward movement of the cords.



FIG. 2. (*C*) Hemilaryngectomy specimen shows the tumor limited to the true cord. (A) False cord; (B) anterior commissure; (C) true cord.



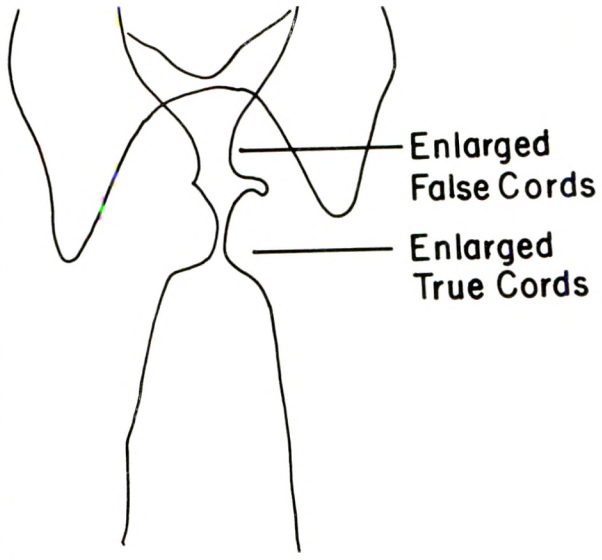


FIG. 3. Benign enlargement of the cords. There is enlargement of the true and false cords. Other roentgenograms demonstrated preservation of the ventricles. Mucosal stripping of the cords showed hyperkeratosis without tumor.

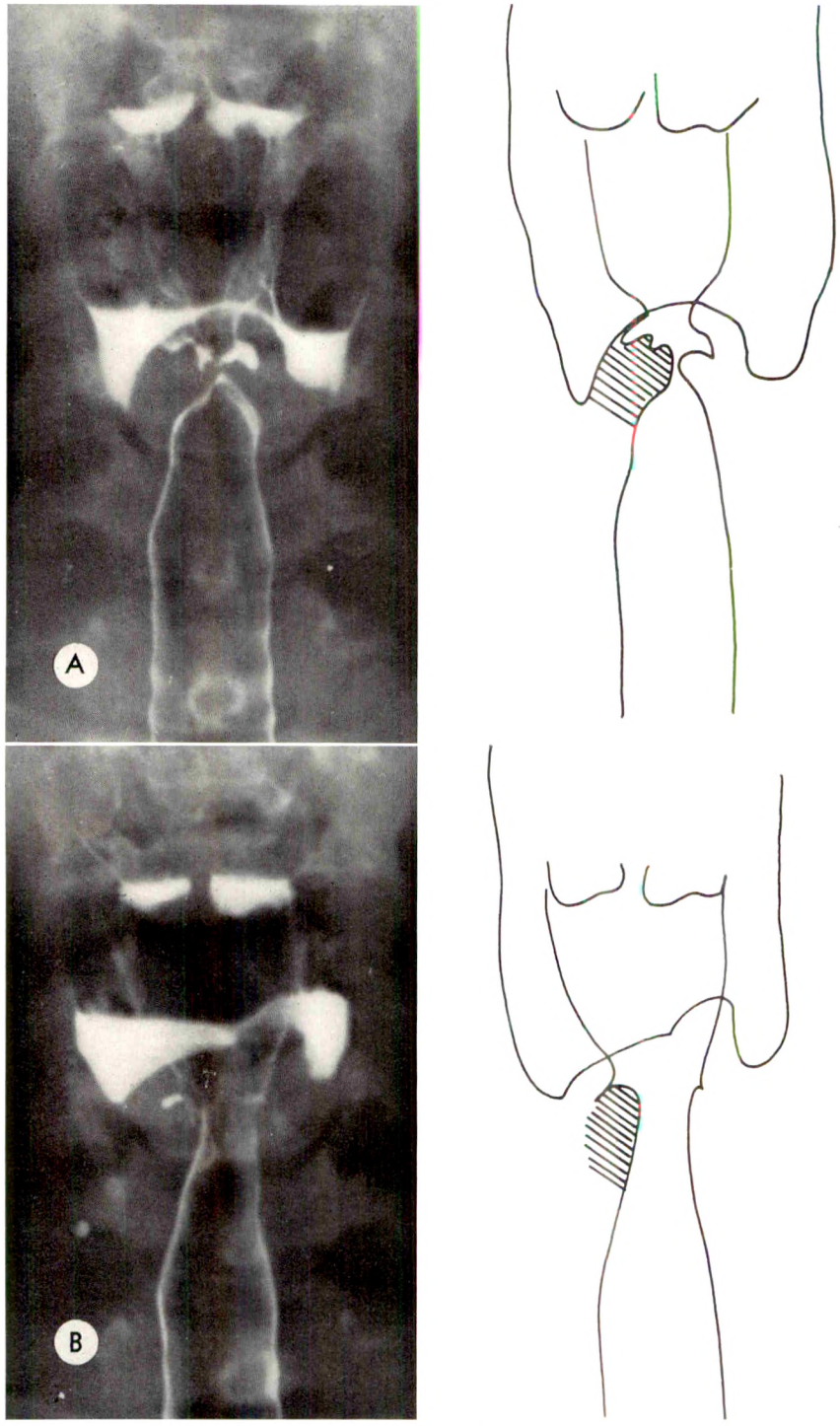


Fig. 2. Carcinoma of the right true cord with fixation. (*A*) *Phonation*. The normal sharp right angled contour between the cords and the trachea is maintained, indicating freedom from involvement of the subglottic area. (*B*) *Inspiration*. The normal left cord has completed retraction during inspiration while the tumor-involved true cord has retracted but slightly. The subglottic area on the involved side slopes gently laterally in contrast to the nearly vertical contour on the normal left side.

Table II

HAAGENSEN'S INDICATIONS FOR MULTIPLE BIOPSIES

I. Internal mammary biopsies of first, second or third interspace are done for:
   A. Tumors of the outer half of the breast measuring 5 cm. or more
      Tumors of the inner half of the breast measuring 3 cm. or more
      All tumors of the center of the breast
   B. When axillary lymph nodes are involved
II. Apex of axilla biopsies are done when more than one axillary lymph node is clinically involved, or if one involved axillary lymph node measures 2.5 cm.
III. Both forms of biopsy are done when any grave clinical sign is present—edema, ulceration, fixation of axillary lymph nodes, or solid fixation of primary tumor to chest wall

sented. A 2 million volt x-ray unit is used which operates at a target skin distance of 100 cm. with a half value layer of 7 mm. of lead. The fields which are utilized are diagrammatically shown in Figure 1.

Included in the fields of radiation are the supra- and infraclavicular areas, the axilla and the internal mammary lymph nodes. The first and second intercostal space of the opposite side is added if the lymph nodes in the first or second interspace on the diseased side are involved. We know that the disease will not frequently metastasize to the opposite internal mammary lymph nodes, but it is felt that inclusion of these lymph nodes in the field of radiation is a worthwhile prophylactic procedure because the lymphatics cross at this level.

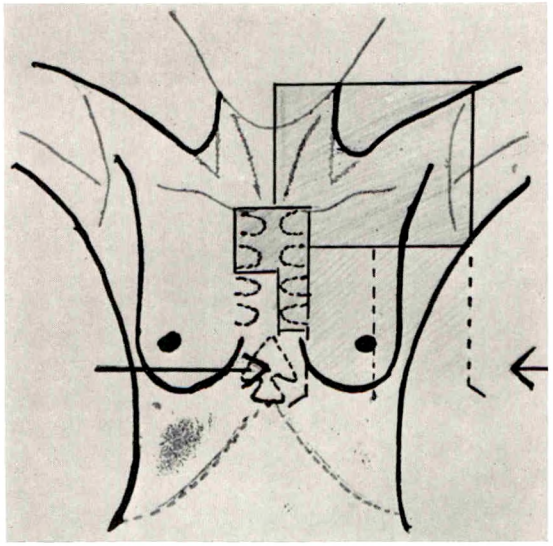


Fig. 1. Diagram showing the treatment fields which are utilized in radiotherapy of patients with primary carcinoma of the breast.

A daily dose of 200 rads is delivered to all fields and a total dose of 5,000 rads is given in 5 weeks. The lymph node bearing areas are treated through 2 anterior fields, while the breast itself is treated through 2 tangential fields in the attempt to save as much lung tissue as possible from the irradiation. No bolus is used in order to avoid an increase in the skin reaction.

It is our purpose to document the exact dosage which is delivered at various levels of the breast from the chest wall to the skin proper with direct readings and have started this procedure in close cooperation with Mr. Richard Mooney, Sr. Physicist of the Department of Physics of the Francis Delafield Hospital in New York. So far we have checked the dose at the point of maximum ionization, that is 4 mm. below the skin, with specially designed condenser ionization chambers, which were placed in the center and on the margins of the fields at different levels. The characteristics of these ionization chambers are shown in Table III.

The direct readings taken with these chambers showed dosages varying from 240 rads at the margins of the fields to a peak of 340 rads in the center of the field when a

Table III

CHARACTERISTICS OF CONDENSER IONIZATION CHAMBERS

Air Volume	0.01 $cm.^3$
Outside Diameter	0.6 cm.
Range	0 to 250 r
Equilibrium Walls	
Calibration for 2,000 kv. radiation by comparison with a calibrated 25 r condenser chamber	

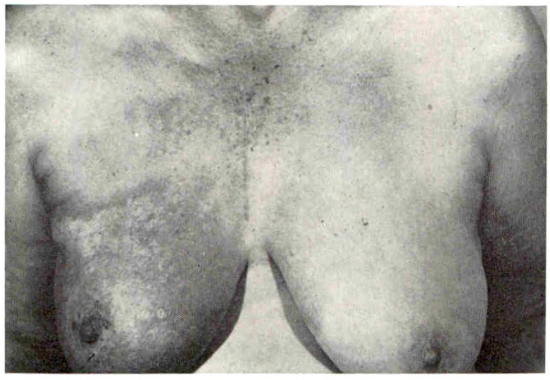


FIG. 2. Photograph showing the appearance of the breast 6 years after radiotherapy.

calculated dose of 200 rads was given throughout the breast. There were, of course, slight individual variations.

During the last years more radiation has been added to the site of the primary tumor in such cases where the immediate response was not completely satisfactory and where further irradiation could be tolerated. This additional treatment is started 2 to 4 weeks after completion of the full cycle of therapy. The roentgen beam is centered directly over the primary lesion with a cone, which is large enough to cover the primary tumor and a 3 cm. margin of surrounding tissue. For this additional therapy a 250 kv. unit, a half value layer of 2.5 mm. of Cu and a target skin distance of 50 cm. have been used in order to keep the additional dose to the lung to a minimum. The intended daily dose is 200 rads for a total additional dose of not more than 2,000 rads, but the single, as well as the total dose, is adjusted according to the individual patient

The immediate tolerance to this amount of radiation has been good and there have been only a few late changes. Figure 2 shows the appearance of the breast treated in this fashion 6 years after therapy. There is, of course, palpable fibrosis, but the scarring is relatively little. The only late side effects of significance which we have observed are radiation changes of various degrees in the lungs and pleura which have been described by us some years ago. These changes usually occurred 3 to 6 months after completion of therapy and were in many instances only demonstrated by a routine chest roentgenogram. Subjective symptoms, like dry cough and dyspnea, have occurred in about 10 per cent of the group.

Table IV shows the distribution of the patients beginning with 1952 through 1958 and also the distribution of the involved lymph nodes in this patient material.

When evaluating any patient group for long term survivals, it is of utmost importance to outline, first, the type of disease and, second, the stage of the disease at the beginning of therapy. This is especially important in an evaluation of patients with

TABLE IV

DISTRIBUTION OF INVOLVED LYMPH NODES

Year	No. of Patients	Involvement of Internal Mammary Lymph Nodes and Apex of Axilla	Involvement of Internal Mammary Lymph Nodes	Involvement of Apex of Axilla
April 1952–53	6	4	1	1
April 1953–54	10	8	1	1
April 1954–55	16	10	4	2
April 1955–56	16	8	5	3
April 1956–57	19	9	7	3
April 1957–58	33	6	12	15
April 1958-Jan. 1959	11	4	4	3
	111	49	34	28

Table V

FOLLOW-UP OF PATIENTS TREATED BY RADIOTHERAPY

Followed	No. of Patients	Alive
3 yr.	111	75 = 68%
4 yr.	100	55 = 55%
5 yr.	67	34 = 50%
6 yr.	48	21 = 44%*
7 yr. and more	32	13 = 41%**

* One patient died of arteriosclerotic heart disease; no evidence of cancer at autopsy.

** One patient died of heart failure after a surgical procedure; no evidence of cancer at autopsy.

Table VI

5 YEAR SURVIVAL RATE OF 67 PATIENTS TREATED BY 2 MILLION VOLT IRRADIATION EXCLUSIVELY

Metastases	No. of Patients	5 Year Survival Rate
Involvement of internal mammary lymph nodes and apex of axilla	39	19–47%
Involvement of internal mammary lymph nodes alone	18	9–50%
Involvement of apex of axilla alone	10	6–60%
	67	34

carcinoma of the breast, as it is well known that there are great variations in the natural course of this disease and that surprisingly long survival periods have been observed in some of the untreated patients. When breaking down our patient material according to type and stage, it should be pointed out that the disease in these patients is characterized by a tendency to spread rapidly and early. This is documented by positive regional lymph node biopsies in spite of the limited size of the primary tumor. These patients had disease which had widely metastasized, a fact which represents a grave prognostic finding, and which will definitely influence the outcome of the untreated disease unfavorably. Such patients will not be found as survivors in a group of untreated patients.

Table v shows the follow-up and survival rate of the 111 patients who were treated with radiotherapy alone. In addition to the 2 patients mentioned in this table, 12 more came to autopsy. Three cases did not show any evidence of cancer whatsoever in the treated areas, neither at the site of the primary tumor nor in the lymph nodes, while in several others the treated lymph nodes proved to be free of disease. This seems to confirm an observation reported in 1958;[4] namely, that it is possible to sterilize by radiotherapy metastatic lymph nodes of various primary tumors as long as the lymph nodes are less than 3 cm. in size and as long as a sufficient dose can be delivered. It is interesting to note that of 67

Table VII

FIVE YEAR RESULTS FOR 34 PATIENTS WITH BREAST CANCER CONSIDERED INOPERABLE BY HAAGENSEN'S TRIPLE BIOPSY CRITERIA AND TREATED BY COMBINED PROCEDURE (URBAN)

Metastases	Total No. of Patients	Alive with No Evidence of Disease	Alive with Disease	Total No. Alive
Int. mam. +; first space −	8	6	0	6
Axilla +; first space +; apex −	6	1	1	2
Int. mam. +; first space −	6	0	1	1
Apex +; first space +	4	1	0	1
Int. mam. +; axilla −	3	1	0	1
Int. mam. −; apex +	7	4	0	4
	34	13	2	15

Int. mam. = internal mammary lymph nodes; first space = first intercostal space; apex = apex of axilla.

TABLE VIII

FIVE YEAR SURVIVAL RATES FOR 67 PATIENTS TREATED BY RADICAL MASTECTOMY WITH BIOPSY OF INTERNAL MAMMARY LYMPH NODES AND SUBSEQUENT DEEP RADIATION THERAPY OVER THE INTERNAL MAMMARY LYMPH NODE AREA (HANDLEY)

Metastases	Total No. of Patients	Alive and Well	Alive with Recurrence	Total No. Alive
Axilla only	34	18	4	22
Internal mammary lymph nodes only	4	3		3
Axilla and internal mammary lymph nodes	29	1	6	7
	67	22	10	32

Twenty-eight of the patients with internal mammary lymph node metastases received postoperative roentgen therapy, 250 kv., 3,000 r–5,000 r tumor dose.

TABLE IX

COMPARISON OF 5 YEAR SURVIVAL

Author	No. of Patients	Type of Treatment	5 Year Survival Rate
Handley	67	Radical mastectomy and irradiation	32–47.7%
Urban	34	"Combined approach"	15–44%
(New Figures)*	100	"Combined approach"	48–48%
Guttmann	67	2 mv. irradiation	34–50%

* Many of these patients were treated with additional postoperative radiation to the lymph nodes in the supraclavicular area.

patients followed for 5 years, the survival rate varied between 47 per cent and 60 per cent, according to the lymph node involvement, but, of course, it is necessary to keep in mind that this series is still relatively small (Table VI).

There is not much possibility for comparison of these results with those obtained by other methods of treatment as only Urban in New York and Handley in England have broken down some of their patient groups according to Haagensen's criteria (Table VII and VIII). Even here, the patient material is not fully comparable. It is, for instance, impossible to tell how many of Handley's patients with positive axillary lymph nodes had actual involvement of the apex of the axilla, a finding, which lessens the chances for a 5 year survival considerably. Although the patient material is broken down in a similar fashion as ours, it is realized that patient material from different hospitals does not lend itself to an entirely accurate comparison.

Table IX shows the 5 year survival rates of patients treated by the different methods. These figures refer in all 3 groups to the number of surviving patients, not necessarily to those free from disease.

CONCLUSION

It is recognized that statistics and percentage figures have to be evaluated with restraint and criticism when the material given is rather small. However, even within these limitations, the results of supervoltage therapy in the treatment of primary carcinoma of the breast are favorable when compared with those using other methods of treatment.

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THE VALUE OF RADIATION THERAPY IN POST-MASTECTOMY LYMPHANGIOSARCOMA*

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MORE than 50 additional cases of lymphangiosarcoma have been recorded in the literature[1–28] since the original report of Stewart and Treves.[29] This lesion has occurred as a relatively rare sequela in the lymphedematous arms of women following radical mastectomy. The cutaneous manifestations appear as bluish purple, soft, and slightly elevated nodules in the skin. They recur promptly after excision and metastasize early and widely. An attempt to control the process has been by interscapulo-thoracic amputation, irradiation, or both; but none has been successful, the disease usually terminating fatally within 2 years of its incipiency. When Southwick and Slaughter[28] in 1955 reported a patient who survived 5 years (now 11 years) following radiation therapy, this modality offered a hope of producing better clinical tesults.

The purpose of this paper is to report the failure in 4 patients who received intensive irradiation using low voltage, high voltage, and supervoltage roentgen rays and high energy electrons. The disease remained uncontrolled although temporary palliation was obtained in each instance.

REPORT OF CASES

CASE 1. L.R., a 69 year old white female, discovered a lump in her left breast in 1932, at the age of 46. She was seen at Memorial Hospital where a diagnosis of carcinoma of the breast was established by aspiration biopsy. Treatment consisted of a course of preoperative irradiation followed in 2 months by radical mastectomy. The histopathology was "infiltrating duct carcinoma without metastasis to the axillary lymph nodes." There followed shortly, pain and swelling in the upper left extremity. Radiation changes in the lungs, ribs and left humerus appeared. In 1950, the patient fell, fracturing the left humerus, which healed without complications.

In 1955, 23 years following radical mastectomy, multiple, raised, compressible lesions with a bluish discoloration, were noted on the left arm (Fig. 1). Excisional biopsy of a cutaneous lesion was diagnosed lymphangiosarcoma, and the patient was referred to the Department of Radiation Therapy for treatment. Three of the nodules were given a single dose of 3,000 rads using 100 kv. peak roentgen rays (half value layer 1.2 mm. Al) at 15 cm. target skin distance. There was moderate regression of these nodules with relief of tenderness after 3 weeks. Irradiation of all the nodules using larger fields was then initiated. A larger medial field, 15×10 cm., and a smaller lateral field, 6×11 cm. were used to treat the involved skin of the upper arm. In a period of 2 weeks a dose of 3,400 rads was delivered. This was with 120 kv. peak (half value layer 3.5 mm. Al) and 20 cm. target skin distance. The course of irradiation was followed almost immediately by moist desquamation (Fig. 2). The skin healed in 6 weeks, using an ointment of triiodothyronine, and the lymphangiosarcoma nodules gradually regressed (Fig. 3).

In January, 1956, the patient was hospitalized elsewhere for bronchopneumonia. In February, 1956, 5½ months after the radiation therapy of the left arm, a recurrent nodule was noted at the periphery of the medial radiation field. It disappeared completely after low voltage irradiation to a dose of 1,500 rads. In June, July and August, 1957, multiple recurrences on the arm developed. These were irradiated through small cones with low voltage. All but one nodule responded well after a fractionated dose of 2,800 rads delivered in a period of 2 weeks. This residual nodule subsequently received an additional dose of 1,400 rads in 3 divided doses.

In September, 1957, the patient developed dyspnea. A chest roentgenogram showed infiltration involving the right middle lung, prob-

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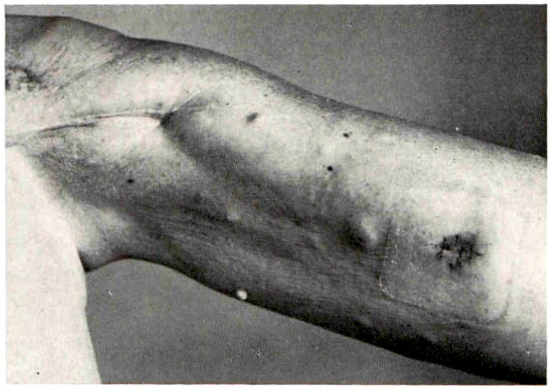


Fig. 1. Case 1. Lymphangiosarcoma of the left arm before radiation therapy. Multiple raised, bluish cutaneous nodules, one of which was recently biopsied, are seen.

ably metastatic. When last seen in October, 1957 the local lesions were inactive but the patient's general condition was deteriorating rapidly. She died at her home of disease on April 15, 1958.

Case II. A.R., a 69 year old white female, had a right radical mastectomy performed at Memorial Hospital in June ,1942, for infiltrating duct carcinoma, Grade II, with metastases to the axillary lymph nodes at Levels I and II. Shortly after the surgery she developed lymphedema of the right arm. She received a course of postoperative radiation therapy to the supraclavicular and axillary areas (250 kv. peak, 2.0 mm. Cu half value layer, 50 cm. target skin distance, 2,000 r in air to each of the anterior and posterior supraclavicular portals and the axillary field) resulting in skin reaction, pulmonary fibrosis and radiation necrosis of a few ribs with fracture.

A tumor was noted in the opposite breast in May, 1949 and 2 months later a radical mastectomy was performed. The histopathology was

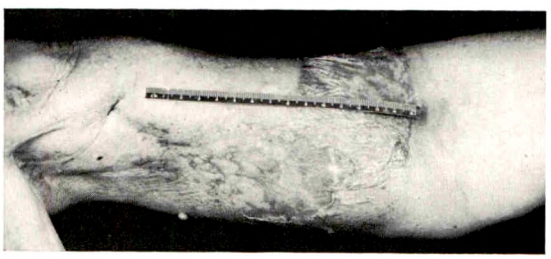


Fig. 2. Case 1. Moist skin reaction is noted after 3,400 rads were delivered in a period of 2 weeks (120 kvp.).



Fig. 3. Case 1. Healing of the skin occurred, and the bluish nodules disappeared 6 weeks after radiation treatment.

"infiltrating duct carcinoma, Grade III, with negative axillary lymph nodes." Because the axillary lymph nodes were uninvolved, the patient did not receive postoperative radiation therapy. Subsequently, however, she developed lymphedema of the left arm.

In December, 1955, an elevated, bluish, ulcerated mass, 4.5×2.5 cm., was noted on the inner aspect of the upper left arm. This lesion was excised at another hospital and was reported as hemangiosarcoma. About one month later, multiple, dark-bluish nodules appeared at and near the site of excision (Fig. 4). The patient was again referred to Memorial Hospital. The slides of the excisional biopsy were reviewed by the Pathology Department of Memorial Hospital and a diagnosis lymphangiosarcoma was made. It was decided to irradiate this area with a single field including all the lesions and a wide margin of seemingly normal epithelium. From February 16, 1956 to March 7, 1956, a dose of 3,400 rads was delivered through a 16×12 cm. field. The physical factors were: 250 kv. peak,



Fig. 4. Case II. Lymphangiosarcoma of the left arm. Multiple dark-bluish nodules at and near the site of excision are seen.

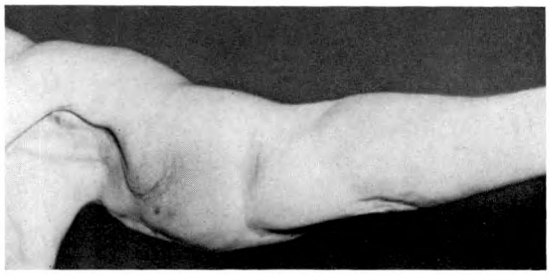


FIG. 5. Case II. Regression of the nodules occurred but pigmentation remained in some lesions after 3,400 rads in 2½ weeks (250 kvp.).

2.0 mm. Cu half value layer and 50 cm. target skin distance. There was marked regression of the tumors but pigmentation remained in some lesions (Fig. 5). In August, 1956, growth was again noted (Fig. 6). In a period of 3 weeks an additional skin dose of 2,900 rads was delivered using the same factors. Most of the lesions disappeared following this course of radiation therapy (Fig. 7). However, many more nodules appeared in the skin of the arm, forearm, and hand. The radiation fields were enlarged accordingly to irradiate practically the entire upper extremity except for the original area which had already received a total of 6,300 rads. A dose of 4,300 rads was delivered in a period of 4 weeks. Moist desquamation was produced and was treated by triiodothyronine ointment but the radiation therapy failed to arrest the disease. The lesions became more extensive after a temporary regression (Fig. 8). In May, 1957, an interscapulo-thoracic amputation was performed. Six weeks later there was evidence of recurrence on the chest wall (Fig. 9). Biopsy of one of the recurrent nodules showed lymphangiosarcoma. The lesions spread widely to involve the chest, trunk, buttock, and thigh. Radiation therapy using 10.4 to 18 mev. electrons depending on the thickness of the lesions was given to many areas for palliation. In January, 1958, she received oncolytic viral treatment using the Egypt 101 isolate of West Nile virus[27] with no significant improvement. The disease progressed rapidly. She developed respiratory distress due to bloody pleural effusion in the left chest cavity and probable bilateral pneumonia. She expired on February 23, 1958. No autopsy was obtained.

CASE III. M.C., a 61 year old white female, was first seen at Memorial Hospital in May, 1943 following the local excision of a tumor in the left breast, diagnosed as infiltrating duct carcinoma, Grade II. A left radical mastectomy was performed. The operative specimen showed metastatic mammary carcinoma to the axillary lymph nodes at Levels I and II; no evidence of residual tumor was noted in the breast. Postoperative radiation therapy was given (1,750 r in air to the left axilla and 2,000 r to the anterior and posterior supraclavicular areas, 250 kv. peak, and 1,500 r in air to the operative field, 120 kv. peak). Four months later, she developed lymphedema of the left arm.

In August, 1956, 13 years post mastectomy, the patient noted a 4 mm. purplish blue nodule on the inner aspect of the upper left arm. Cutaneous biopsy was reported showing lymphangiosarcoma. A wide local excision of the area was carried out. Three months later there was recurrence in the scar (Fig. 10). A forequarter amputation was advised but refused by the patient. It was then decided to irradiate the entire

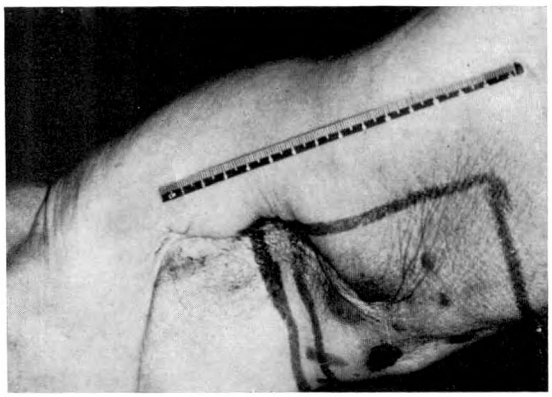


FIG. 6. Case II. Recurrence of the lesions was noted 5 months after radiation therapy.



FIG. 7. Case II. Regression of the lesions occurred after additional 2,900 rads delivered in 3 weeks (250 kvp.).

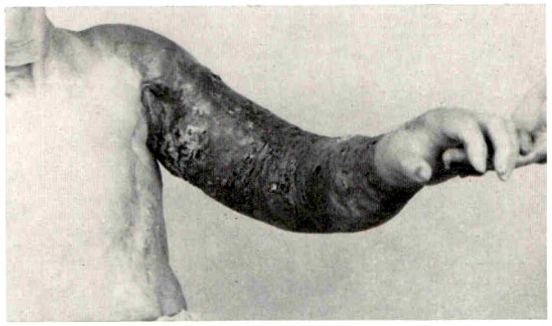


Fig. 8. Case 11. Extensive involvement of the extremity. A dose of 4,300 rads to the entire arm and forearm failed to arrest the disease. This arm was subsequently amputated.

arm using supervoltage radiation with opposing fields even though the recurrence seemed to be superficial and localized at the site of the excision. In a period of 5 weeks beginning November 8, 1956, a dose of 4,900 rads was delivered. The physical factors were: 1,000 kv. peak, 3.4 mm. Pb half value layer, and 100 cm. target skin distance. The size of the bolused opposing fields was 29×18 cm. There was complete clinical regression of the cutaneous recurrence (Fig. 11). Within a months new lesions appeared on the forearm. The entire forearm was also irradiated through 2 opposing fields at 250 kv. peak giving a dose of 4,800 rads. Again there was complete regression of the lesions. Two months later, new lesions were noted on the anterior chest wall, one of which was biopsied and showed metastatic mammary carcinoma. These were treated by low voltage therapy. In April, 1957, the lymphangiosarcomatous lesions recurred on the left arm, the site of previous intensive irradiation (Fig. 12). The disease spread rapidly to other parts of the body. In June, 1957, she received Egypt 101 virus inoculation[27] with some subjective and objective improvement for approximately 2 months. Many symptomatic nodules were also given low voltage therapy, averaging 1,000 to 1,500 rads. In October, 1957, she was given nitrogen mustard, triethylenemelamine, and cortisone in an attempt to suppress her immune reaction to the virus so that a second course of virus therapy could be given. The treatment, however, resulted in severe pancytopenia, fever, and bleeding. The patient expired on November 20, 1957, despite intensive supportive treatment.

Postmortem examination showed extensive metastatic and recurrent lymphangiosarcoma in the skin. The lesions were composed of hemorrhagic, friable nodules extending through the full thickness of the skin into subcutaneous fat. There was hypoplasia of bone marrow probably due to chemotherapy and multiple hemorrhages into lungs, kidneys, ureters, bladder, adrenals and subarachnoid space.



Fig. 9. Case 11. Recurrence on the chest wall was noted 6 weeks after interscapulo-thoracic amputation.

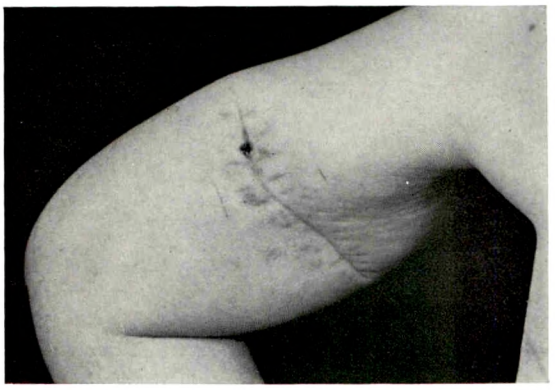


Fig. 10. Case 111. Lymphangiosarcoma of the left arm. Bluish nodule at the site of wide local excision is seen.

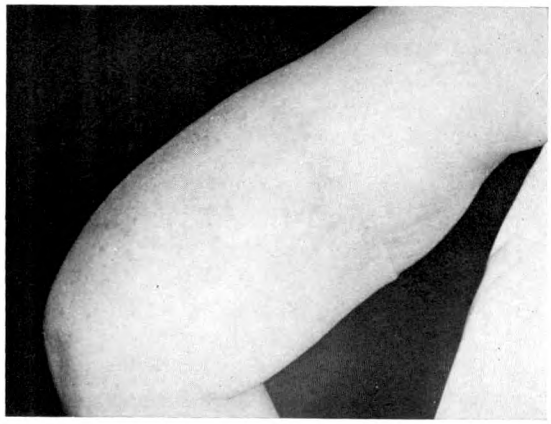


FIG. 11. Case III. Complete regression of the cutaneous lesion followed after irradiation of the entire upper arm, 4,900 rads in 5 weeks (1,000 kvp.).

CASE IV. S.K., a 34 year old female, first noted a lump in the left breast in July, 1947. A left radical mastectomy was performed on September 3, 1947, the laboratory report showing "infiltrating duct carcinoma of the apocrine type with positive axillary lymph nodes at Levels II and III." She received postoperative radiation therapy (2,000 r in air to each of the anterior and posterior supraclavicular areas, and 1,750 r to the axilla, 250 kv. peak, and 1,500 r to the anterior chest wall, 120 kv. peak).



FIG. 12. Case III. Recurrence of lymphangiosarcomatous lesions on the left arm developed 5 months after radiation therapy.

Within a year the patient developed persistent lymphedema of the left arm. In 1949, she had a suppurative process in the arm, probably infection in the epitrochlear lymph node which after drainage promptly healed. In November, 1957, 10 years after radical mastectomy, a reddish blotch appeared on the skin of the upper left arm. She consulted a blood specialist, blood studies were done and she was reassured. Approximately 2 months later, the reddened area ulcerated and a fungating tumor appeared. She was told by her physician that this was "a blood clot" and "as soon as it was extruded, the arm would clear up." When the patient was seen at Memorial Hospital in February, 1958, there were ecchymotic areas, varying from 4 to 10 mm. in diameter, involving the entire upper extremity. There was a fungating tumor, 8×5×4 cm. in size, in the upper arm. There was also a smaller fungating mass superior and lateral to the larger one (Fig. 13). On February 22, 1958, a left interscapulo-thoracic amputation was performed. In October, 1958, recurrent nodules appeared on the left chest wall (Fig. 14). She was then given a course of high energy electron beam irradiation. The left anterior and the left lateral chest walls were irradiated through three 15×15 cm. fields. In a period of $5\frac{1}{2}$ weeks each area received a maximum dose of 5,800 rads using 10.4 mev. electrons. There was brisk erythema and the lesions disappeared completely. In December, 1958, a 2 mm. skin nodule developed at the lower end of the amputation scar at the margin of the field of irradiation. This lesion was given, 1,800 rads in 4 divided doses through a 3 cm. cone, also

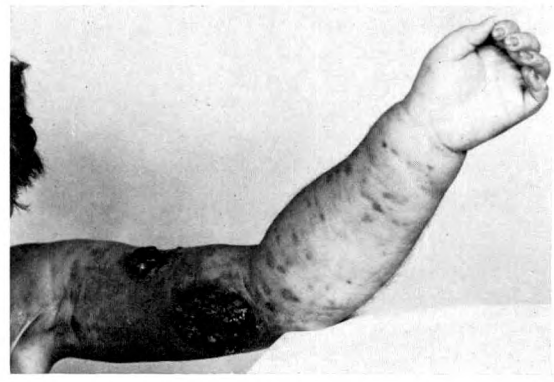


FIG. 13. Case IV. Lymphangiosarcoma of the left arm. Numerous cutaneous nodules and two fungating masses with ulceration are seen.

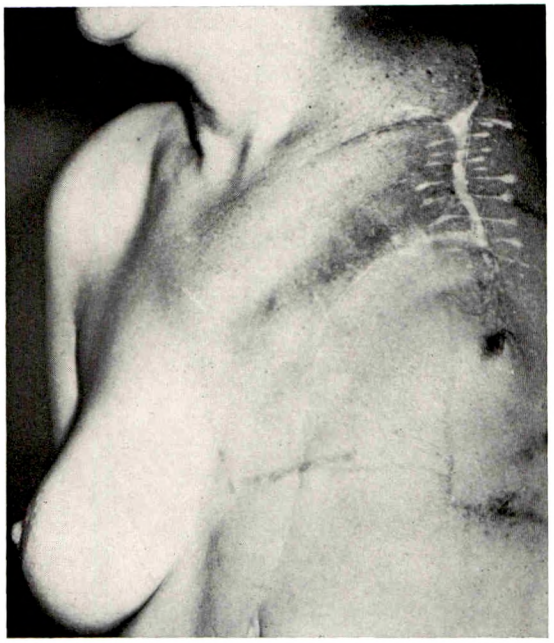


Fig. 14. Case IV. Reccurrence on the chest wall was noted 4 months after interscapulo-thoracic amputation.

utilizing 10.4 mev. electrons. In January, 1959, the patient was admitted to another hospital with an enlarged liver, icterus and ascites. She died at home shortly thereafter.

DISCUSSION AND CONCLUSIONS

There is no doubt that irradiation produces regression of cutaneous lymphangiosarcoma. The regression, however, is usually short-lived. The lesions not only metastasize widely, but also recur locally within the fields of intensive irradiation after heavy doses. In the 4 patients reported here, the irradiation was carried to a dose of from 3,400 rads in 2 weeks to 5,800 rads in $5\frac{1}{2}$ weeks, using various types of radiation (low, high, and supervoltage roentgen rays and high energy electrons). The dose was high enough to produce moist skin reaction in some areas and yet failed to permanently control the disease locally or prevent systemic spread.

Of more than 50 patients with lymphangiosarcoma recorded in the literature,[1–28] 3 patients survived over 5 years; one of these had forequarter amputation,[1] one had forequarter amputation followed within the year by excision of a recurrence,[4] and one had irradiation.[28] With a rare tumor such as this, the survival of one patient following radiation therapy and 2 following interscapulo-thoracic amputation probably does not yield meaningful information for management of future cases. Certainly, the first 3 patients presented here received as much or even greater amounts of irradiation than the case reported by Southwick and Slaughter.[28] Interscapulo-thoracic amputation in one of our patients and in over 20 reported instances failed to control the disease.

McConnell and Haslam,[21] based on the histologic examination of the specimens obtained from biopsies of 3 cases, amputation of arms of 2 patients, and autopsy of one of their 5 patients with lymphangiosarcoma, described multiple foci of angiomata. Some of the angiomata were undergoing various states of malignant change. According to them, the course of development of the lesions may be divided into 3 stages although considerable overlapping was observed: a prolonged lymphedema, premalignant angiomatosis, and frankly malignant angiosarcoma. Is it possible that the longer survival of some patients is due to early or less malignant type of disease rather than to the efficiency of the treatment—surgical or radiotherapeutic?

From the study of the 4 patients who form the basis of this report, one fact stands out. Irradiation offers good palliation. The lymphangiosarcomatous lesions tend to be painful and untreated progress to ulceration. Radiation therapy will ameliorate the symptoms, and frequently reduce the size of the tumors.

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ULTRASOUND IRRADIATION OF THE HYPOPHYSIS IN DISSEMINATED BREAST CANCER*

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INVESTIGATIONS concerning the interactions of ultrasonic energy* with tissue have led to the recognition of three general areas of clinical usefulness: diagnosis, diathermy, and modification of tissue structures.[6,9] The use of ultrasound to modify anterior pituitary glandular function for the palliation of advanced breast cancer rests within the last category.

Modification of tissue structure and/or function at internal body sites is accomplished by delivering focused high level precisely controlled ultrasound into the structures to be modified. Marked focal effects may be produced at a desired depth without damaging intervening tissue. This requires accurate control of dosage parameters and the sites of irradiation. The ultrasonic energy levels delivered to a tissue site within a few seconds are of a considerably higher order than those used in diagnosis and diathermy. For example, the levels currently employed to produce selective changes in the tissue components of the central nervous system lie between 100 and 2,000 watts/cm.^{2} and the durations of the exposure lie generally in the range from $\frac{1}{2}$ to 5 seconds.[5] The frequency of the ultrasound employed in the present human study was 980 kc./sec. In specifying the acoustic parameters of radiation, the acoustic particle velocity amplitude† is specified since it is the measured quantity rather than intensity. The amplitude was 350 cm./sec. and the duration of the exposure 2.5 seconds to 3.0 seconds at each site in the array. The interval between successive exposures was 2 minutes. The selective tissue action of interest here is produced by a nonthermal mechanism, with a positive temperature coefficient.

* Sound above 20 kc./sec. frequency.

† The particle velocity amplitude is the maximum value of the sinusoidally varying particle velocity of the medium.

PURPOSE

Effective palliation for disseminated mammary cancer is obtained through hormonal alterations by the use of exogenous drugs and ablative procedures of endocrine glands (adrenals, pituitary, and gonads). This study was designed to seek another potential method of hormonal palliation in advanced breast cancer; namely, using focused, high intensity ultrasound as the therapeutic tool.

In considering pituitary glandular destruction, the normal adult human hypophysis appears little changed by roentgen radiation in tissue doses up to 10,000 roentgens.[10] However, the implantation of ionizing energy sources within the pituitary and/or its fossa appears quite destructive.[12] Likewise, proton beams from an external source can destroy the gland[3,13] and surgical extirpation is effective.[16] With respect to surgical hypophysectomy, Van Buren and Bergenstal[17] have reported that a complete surgical hypophysectomy is not essential to induce regression in mammary cancer.

It was felt that a "partial" hypophysectomy might be readily accomplished with focused ultrasound and that it could be used repetitively upon a given patient, quickly and without discomfort. After a preliminary animal study,[11] 5 female pa-

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tients with microscopically proved advanced breast cancer were selected for the investigation. The patients, families, and referring physicians were fully apprized of the procedural aspects and their willing concurrence and cooperation enlisted. The intent was to follow each patient in detail for the remainder of her life. A case report of each patient and more detailed procedural descriptions and assay were presented in a prior publication.[7]

TECHNIQUE OF IRRADIATION

Focused high intensity ultrasound has been used in the past decade in neurologic research on experimental animals at the Biophysical Research Laboratory of the University of Illinois, and, more recently, in a joint human research project by that laboratory and the Division of Neurosurgery at the State University of Iowa. In the human studies, the pathogenetic mechanisms underlying various disorders have been under scrutiny, *e.g.*, those germane to the tremor and rigidity of Parkinson's disease, the various involuntary movements of cerebral palsied patients, intractable pain, and the dysesthesias and dyskinesias which sometimes follow cerebral vascular accidents.[14] A single attempt at the destruction of an intracranial interpeduncular tumor has been made.

The pituitary gland irradiation was implemented in the advanced mammary cancer patients in a manner similar to the irradiation of brain structures. The technique is as follows: Because ultrasonic energy cannot penetrate the cranial bone without undue absorption, reflection and refraction, a lateral craniectomy is performed 2 to 3 weeks prior to irradiation. The scalp and muscles are repositioned by suture and the bone is saved for later replacement. The aperture in the calvarium is approximately 8×10 cm. and can accommodate the four converging beams from the four-beam focusing ultrasonic irradiator.

Precision focal irradiation is essential (Fig. 1). To secure site-specific localization, the patient's head is held immobile in a stereotaxic head holder. This is accomplished by the use of four stainless steel supporting rods which fit into superficial skull burr indentations made through short scalp incisions. The entire procedure may be performed during local or light general anesthesia and light sedation. The four-beam focusing transducer is supported and moved by an overhead calibrated carriage with a positioning accuracy of 0.1 mm. From calculations made using roentgenographic measurements, anatomically repetitive irradiation procedures can be accomplished. It is necessary also to employ a liquid transmitting medium (degassed saline) to conduct the acoustic energy from the irradiator to the skin.

The equipment described here is primarily intended for the modification and treatment of neurologic disorders, *i.e.*, for the irradiation of very small volumes of tissue. In the instance of the hypophyseal gland, 14 to 35 sites in the gland were successively exposed to the focused ultrasound as a three dimensional array to uniformly irradiate the glandular volume.

COMPLICATIONS OF ULTRASONIC IRRADIATION

Either as a consequence of direct or indirect irradiation of contiguous structures,

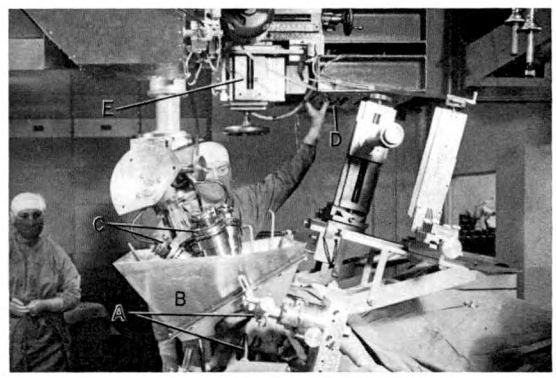


FIG. 1. The ultrasonic equipment is shown in the operating room. The patient's head is secured in the stereotaxic head holder (A). The transducers (C) are immersed in the degassed saline transmitting bath (B). The carriage control panel (D) and overhead positioning carriage are shown (E).

or of bone heating adjacent to the sella turcica, several complications resulted. These were regarded as sufficiently serious that we elected not to pursue the technique further until more suitable instrumentation is available. Each patient showed polyuria (anticipated) and, in 5 of the 6 irradiation sequences, recoverable palsies of the extra-ocular muscles (oculomotor and abducens nerves) ensued. Two patients developed severe visual changes: monocular blindness in one and a left homonymous hemianopsia in the other. One patient developed a right hemiplegia, probably in consequence of the ultrasound traversing recently traumatized tissue (degassing phenomenon). Another patient developed an upper extremity paresis due to a vascular accident, likely unrelated *per se* to the radiation.

OBSERVATIONS AND DISCUSSION

The earlier observations, including assay and procedural descriptions, have been reported. Longer term observations are now available, particularly upon 2 patients, one followed for 17 months to death with autopsy, and the other for 19 months to an approaching terminal state. This latter patient was 1 of 2 patients in whom a growth acceleration occurred after irradiation. These will be commented upon. In no instance was a favorable control of the cancer growth accomplished.

To sum up the *endocrine observations:* In each instance after irradiation an increased urinary excretion of 17-ketosteroids occurred. This lasted a median time of 2–4 days, after which normal values reappeared. In contrast, similar measurements in two sham-type operations (craniectomy and a uterine cervical dilatation and curettage) failed to produce this effect; however, the craniectomy was performed during deep anesthesia, and thus this procedure might not be strictly comparable to the others. To continue, transient depressed indices of thyroid function occurred after ultrasonic irradiation; the serum protein-bound iodine values and the thyroid radioiodine uptake determinations dropped sharply, then regained normal levels after a period of about 4 weeks. No patient developed myxedema from pituitary dysfunction. By contrast, after surgical hypophysectomy no such thyroid rebound or regain phenomena occurred. The gonadotrophin determinations showed no consistent pattern, but long-term observations demonstrated continued, although lowered, excretion levels. All patients developed diabetes insipidus at 3–7 days after the ultrasonic irradiation with a varying recovery rate toward normal after a few weeks. The fifth patient had more severe diabetes insipidus (7 liters daily of urine) and recovery was delayed for several months.

Periodic selected endocrine studies during 16 months and a complete autopsy examination were made upon a *twice* irradiated 64 year old patient. This patient continued to secrete gonadotrophins, modest declining amounts of 17-ketosteroids, and maintained an essentially normal thyroid status. Adenohypophyseal and neurohypophyseal function was evident to within 2 months of death. She died of the neoplasm after a terminal hospitalization in another city and we were permitted a complete postmortem examination.

The pituitary gland was found severely withered within the fossa (Fig. 2). However, on microscopic examination (Fig. 3), a small amount of viable anterior lobe pituitary tissue with patent vasculature was demonstrable. The neurohypophysis was similarly reduced in size. The adjacent bone was intact.

Microscopic studies of the tissues removed from 2 other patients by surgical hypophysectomy 6 and 14 weeks after ultrasonic irradiation showed modest central scarring and peripheral coagulation damage of the anterior glandular hypophysis. The coagulation damage was adjacent the bone. Both removed pituitary glands were judged grossly at surgery to be reduced to approximately 70–80 per cent of the estimated original size.

To summarize the *anticancer influences* after irradiation: No patient was benefited as a consequence of the ultrasonic irradiation other than in such a manner as would accompany increased care. This result does not militate against other efforts using this form of energy directly or indirectly in cancer diagnosis[15,18] and/or treatment.[1,2,4,8,19]

COMMENTS ON ACCELERATED CANCER GROWTH

In 2 patients, ages 66 and 46 years, there was acceleration of the neoplastic growth. In the older patient our postradiation observations were brief since she died 3 weeks after a conventional surgical hypophysectomy implemented as an urgent therapy 2 months after ultrasound irradiation. She presented with inflammatory breast carcinoma and during the preceding 2 years had had roentgen therapy, later oral stilbestrol, and then injected androgens. Preceding the ultrasound irradiation she had been on an inconstant regimen of 200 mg. of testosterone weekly. The last injection (100 mg.) had been given her 17 days before the ultrasound procedure during a period designated by us as a free therapeutic interval. Because of travel and other schedules we could not delay. The patient had a relatively small numerical array of 14 ultrasonic exposures which resulted in a relatively greater spacing between irradiation sites. She exhibited the described (but muted) pituitary target organ responses, including clinically mild diabetes insipidus. The cutaneous spread of the cancer began to accelerate rapidly and thus conventional surgical hypophysectomy was implemented to attain control. The gland was moderately scarred and reduced in size. This accelerated growth of cancer was judged significant, for by photographic documentation there had been no significant cutaneous changes in 8 months, but the withdrawal of exogenous testosterone only 17 days before the ultrasound therapy renders this interpretation somewhat ambiguous.

The final patient in the series, 46 years of age, was in a premenopausal status; she was of an inattentive disposition, but it was reliably determined that she had had no prior therapy and had endured the tumor for at least a year, probably much longer. In addition to the breast replacement by cancer, she also had widespread osseous metastases. Fortunately, pre-operative photographs were made 3 weeks and

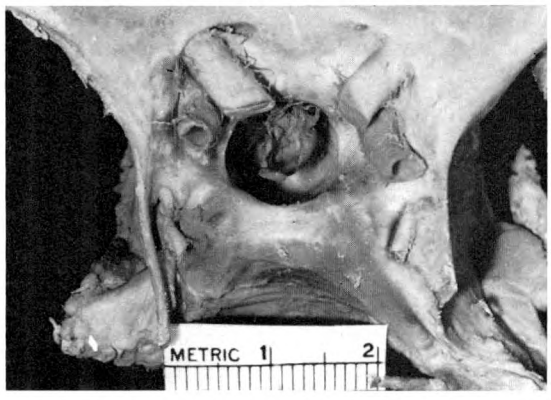


Fig. 2. This pituitary gland had been twice irradiated by 26 and 28 geometrically spaced exposures of ultrasound 8 months apart, the last 9 months prior to autopsy. The atrophied gland exhibited adenohypophyseal and neurohypophyseal function.

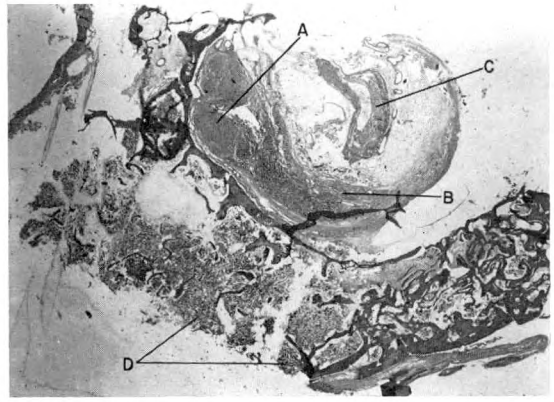


Fig. 3. The microscopic pattern of the hypophyseal gland in its fossa is seen; this is an anteroposterior section of the gland as seen in Figure 2. (A) Neurohypophysis; (B) adenohypophysis; (C) patent blood supply; and (D) essentially normal bone. Technical difficulty was experienced with the *in situ* fixation and hence the shredding artifacts of the bone.

1 week before the irradiation and these helped confirm the history of a minimal but conspicuous recent change in the cancer growth pattern within the breast. Following irradiation delivered to 35 spaced sites within the pituitary gland, a rapid aggressive growth of the cancer appeared in the breast and thorax. In this instance, the further attempt at neoplastic control was through transabdominal surgical adrenalectomy and oophorectomy. By the seventeenth day following adreno-oophorectomy, cancer regression in the described soft tissues was striking. The breast became healed, soft and pliable as the regression continued. The sequence of events covering 16 months is shown in Figure 4, *A–H*. The osseous metastases proved more difficult to judge. The patient had suffered a hemiparesis as a radiation complication with subsequent disuse changes in the bone; moreover, as time passed, the bony response to cancer was of an osteoblastic type, quite difficult to assess. This patient is now approaching a terminal state because of renewed tumor growth, 16 months after removal of the ovaries and adrenals. Hormonal measurements following adreno-oophorectomy revealed, upon withdrawal of exogenous corticoid sources, sharply reduced urinary ketosteroid excretion levels (to less than 1 mg. per gm. of creatinine) and a functioning pituitary, as determined indirectly by the indices of normal thyroid function and directly by wavering excretion levels of gonadotrophins. The tumor growth responses after ultrasonic irradiation and later, after ablation of the ovaries and adrenals, were remarkably different.

The last 2 patients merit additional comment. Very likely they possessed neoplasms exquisitely sensitive to hormonal manipulation. One of them had had 10 months of benefit while on oral stilbestrol; however, because the injected androgen caused fluid retention, it was not administered regularly and was regarded as of little benefit.

The second patient of the two cited exhibited obvious acceleration of the cancer growth following irradiation. After removal of the adrenals and the ovaries such growth was favorably retarded. In relationship to these phenomena, such release from regulatory forces prompts interesting specula-

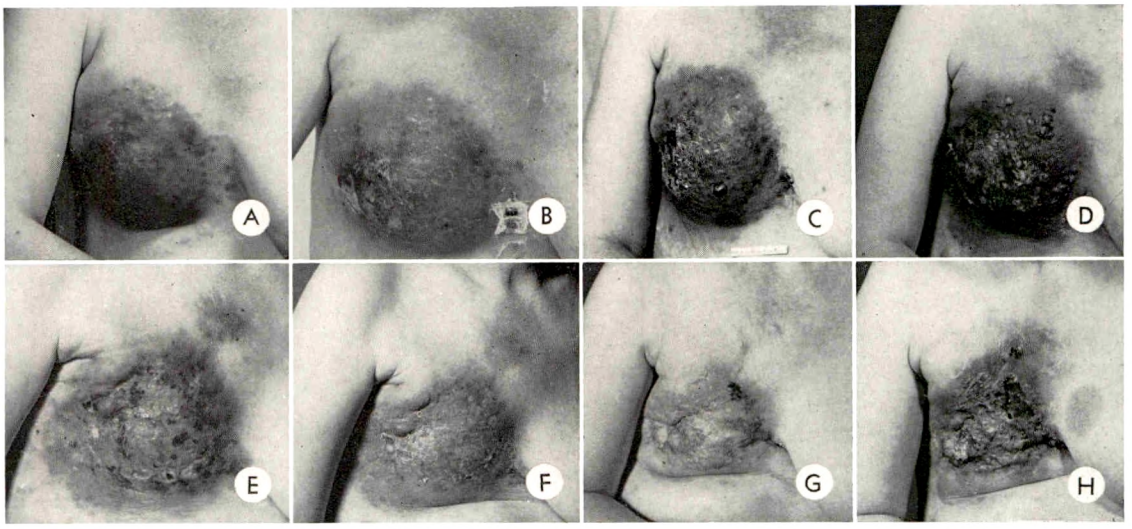


FIG. 4. This pictorial sequence portrays the increased mammary cancer growth after ultrasonic irradiation of the pituitary gland in Patient 5. The continuum shows also the striking response to adrenal and ovarian ablation. (*A*) Three weeks and (*B*) 1 week pre-ultrasonic irradiation of pituitary, (*C*) $4\frac{1}{2}$ weeks post irradiation, (*D*) 12 weeks post irradiation and 2 days pre-adreno-oophorectomy, (*E*), (*F*), (*G*) and (*H*) $2\frac{1}{2}$ weeks, 5 weeks, 8 months, and 12 months post-adreno-oophorectomy.

tion as to the interplay of quantitative and qualitative hormonal factors and their potential for augmenting, deterring, or otherwise modifying on-going cancer processes. The observations attest again to the lack of autonomy in breast neoplastic growth.

SUMMARY

The purpose of this study was the initial exploration of a possible new method for controlling disseminated mammary cancer. Focused ultrasonic irradiation was employed to produce pituitary tissue alterations and, thus, regulatory control of cancer growth by endogenous hormonal changes. Using a technique previously developed for modifying brain structures by precisely controlled ultrasonic energy, 5 patients were irradiated in 6 sequences.

Following irradiation, transient measurable alterations in the hormonal output of certain pituitary target organs as well as diabetes insipidus occurred. No control of the mammary cancer was seen; hence, the primary objective was not attained. Since stimulation of the cancer followed irradiation in 2 patients, it appeared that a loss of a regulatory mechanism took place. The hastened cancer growth was controlled by ablative adrenal and ovarian surgical removal in one patient; the other failed to withstand surgical hypophysectomy and, thereby, was insufficiently observed. No suggestions regarding basic mechanisms to explain the observed changes have been forthcoming.

The exploitation of ultrasonic radiation in the study of the human hypophysis is limited at this time by the lack of instrumentation specifically designed to irradiate the hypophysis without inducing neurologic complications. Such instruments can, we are confident, be designed.

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THE MANAGEMENT OF ADENOCARCINOMA OF THE CERVIX*

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ADENOCARCINOMA of the endocervix is a diagnosis often arrived at with a great deal of difficulty and established only at hysterectomy or autopsy.

The difficulties are:

1. *The site of origin of the disease:*

There may be simultaneous, separate carcinomas of the endocervix and endometrium of distinctly different cell types, or an extensive single process involving the uterine cervix and fundus.

2. *Postradiation endometrial carcinoma:*

A second uterine malignancy may occur years after the primary radiation therapy for carcinoma of the cervix. In such instances, surgical intervention may be complicated by radiation induced endarteritis and fibrosis. However, considering the insidious nature of endometrial carcinoma and the growth attenuating effect of previous radiation for cervical cancer, this may be only an unrecognized form of the first stated problem.

PROBLEMS IN TREATING ADENOCARCINOMA OF THE CERVIX

There appears to be sufficient irregularity in the experience in treating adenocarcinoma of the endocervix that the radiation therapist should pause to reflect before following well-established patterns used in treating squamous cell carcinoma of the cervix. Radiation sensitivity of the primary lesion differs from that of epidermoid carcinoma in the opinion of some, while others believe that the two histologic types respond equally well. Kottmeier[2] reported that although adenocarcinoma is considered radioresistant by many, "Experience at the Radiumhemmet suggests that there is no special type of cancer which is radiosensitive." Kottmeier's view is supported by Gusberg and Corscadan,[6] who based their opinion on findings that the disappearance of the primary lesion in the immediate post-treatment period takes place at a similar rate for both adenocarcinoma and squamous cell carcinoma of the cervix. Buschke[3] reported that adenocarcinoma was so radioresistant that hysterectomy should be done post irradiation in selected cases.

The following case presentation illustrates many of these considerations.

ILLUSTRATIVE CASE

CASE 1. A 49 year old saleslady experienced intermenstrual spotting of 2 months' duration. The gynecologist found that the cervix was enlarged to 6 cm. in diameter and had an irregular granular surface. The uterus was slightly enlarged and a fibroid protruded from the posterior surface. A biopsy (Fig. 1) was reported as epidermoid carcinoma. Since the vaginal fornices and the parametria were uninvolved, she was classified as Stage 1.

She was treated with transvaginal roentgen therapy and intrauterine radium. Four years later, following a sudden gush of watery, blood-tinged discharge, a dilatation and fractional curettage were performed. A large amount of mucinous material was obtained from the endocervical canal. The endometrium was atrophic and yielded little tissue for biopsy. The curetted material (Fig. 2) was reported as adenocarcinoma of endocervical origin.

At hysterectomy an extensive adenocarcinoma of the endometrium involving the myometrium and extending into the fallopian tubes was found (Fig. 3). The cell type (Fig. 4) was unmistakably fundal in character.

Her recovery from surgery was uneventful and she is still well, $13\frac{1}{2}$ years after the initial radiation therapy for epidermoid carcinoma of the cervix and 9 years after hysterectomy for adenocarcinoma of the cervix and endometrium.

The differentiation between squamous and adenocarcinoma of the cervix is seldom

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difficult for the pathologist. There is a diagnostic problem, however, in differentiating adenocarcinoma of the endocervix from that of the endometrium. The difficulties encountered in these instances are well presented by Gusberg and Corscadan.[6] There are several factors which are frequently of aid:

1. Endometrial carcinoma is comparatively rare before menopause.

2. The site of the origin of the tissue obtained by fractional curettage for biopsy is a clue, but many problems may be incurred. Dilatation may spread the tumor tissue from the endocervix into the endometrium and the endometrial carcinoma may be curetted down into the endocervix.

3. Differences in cell shape (columnar or cuboidal) in endometrial and endocervical tissues are present in normal organs, but often are inadequate for differentiation in malignancies.

4. While the glands of the endocervix characteristically produce mucin and those of the endometrium do not, in malignancy the character of the vacuoles in the cytoplasm is often indeterminate, even with mucin stains.

To add to this confusion, the endocervical malignancy can invade the myometrium or vice versa.

The difficulty of determining the presence of a fundal carcinoma when a cervical adenocarcinoma is diagnosed is illustrated by the following case.

ILLUSTRATIVE CASE

Case II. A 64 year old housewife presented with genital bleeding of one week's duration. Fractional curettage was reported as adenocarcinoma of endocervical origin and polypoid endometrial hyperplasia. Following radium therapy, a hysterectomy was performed at the appropriate time. The histologic report of the surgical specimen was adenocarcinoma of the endometrium with postirradiation changes and polypoid endometrial hyperplasia. Two years after hysterectomy, she developed a recurrence in the vaginal vault. This was excised with ade-

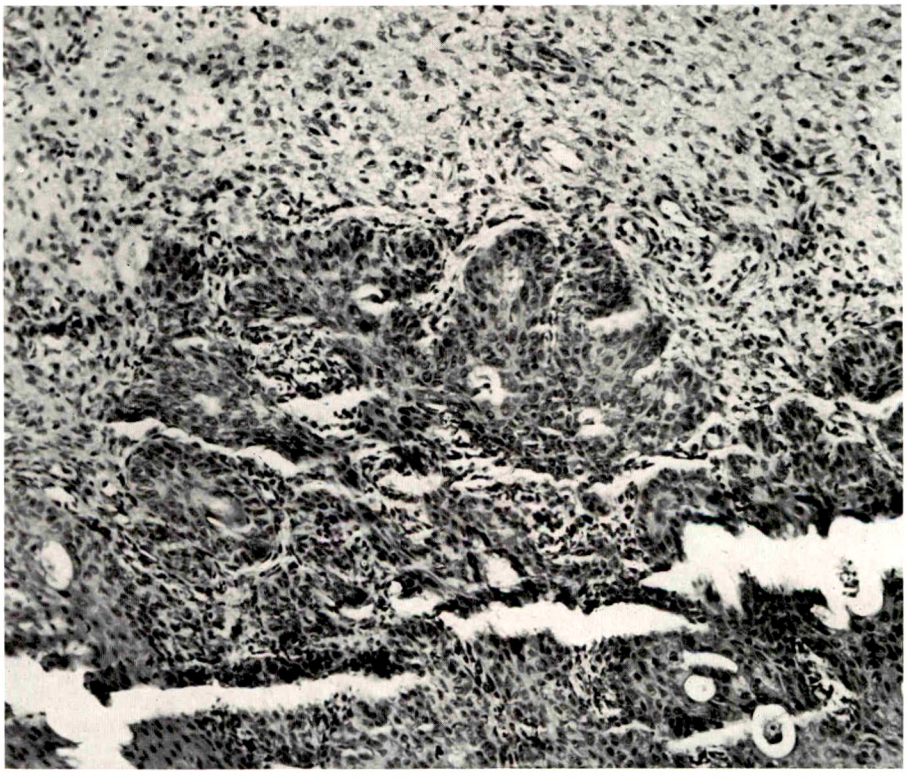


Fig. 1. Case 1. Biopsy specimen of the cervix demonstrating invasive epidermoid carcinoma at the time of original treatment planning.

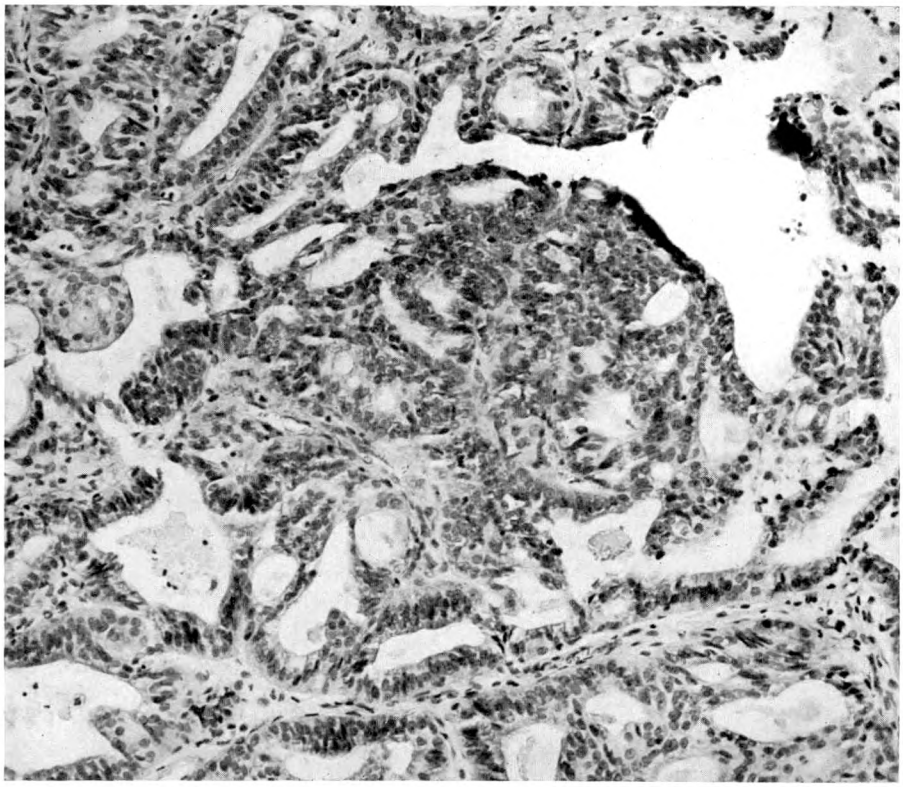


FIG. 2. Case 1. Specimen from endocervical curettings 4 years after previous treatment with radiation demonstrating invasive adenocarcinoma. There is little similarity between this and Figure 1.

quate surgical margins, but the patient died 2 weeks postoperatively of coronary occlusion.

The treatment problem arising in a case of adenocarcinoma of the endocervix with a simultaneously occurring endometrial carcinoma which is undetected by pre-radiation studies is illustrated by this case. The importance of the problem is emphasized by the fact that 4 out of 9 patients with adenocarcinoma of the endocervix who had elective postirradiation hysterectomy were found to have endometrial carcinoma in the surgical specimen (Table 1).

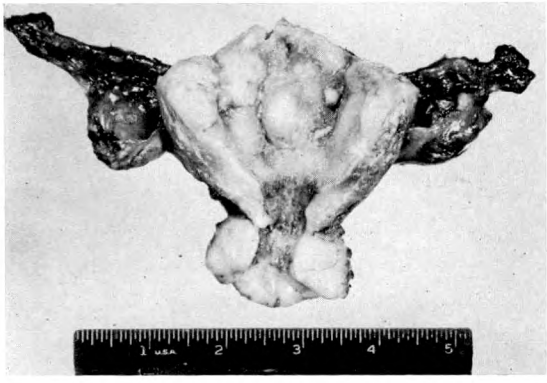


FIG. 3. Case 1. Surgical specimen showing extensive involvement of the upper portion of the uterus at the orifice of the fallopian tube extending deeply into the myometrium and the rather discretely separated deformities of the endocervix, the site of the biopsy specimen shown in Figure 4.

There were 26 patients with endocervical adenocarcinoma on whom elective surgery was not performed after radiation therapy. The survival rate at 5 years was 10 out of the 22 patients who were diagnosed prior to 1957. Of the 4 cases in which the second disease was discovered late in their follow-up, none was salvaged by subsequent surgery (Table II).

Ackerman and del Regato[1] and Henriksen[7] have stated that the principal chain of spread of carcinoma of the cervix is through the lymphatics of the parametria to the external iliac and hypogastric regions. Therefore, complete irradiation is emphasized in any adenocarcinoma of the uterus

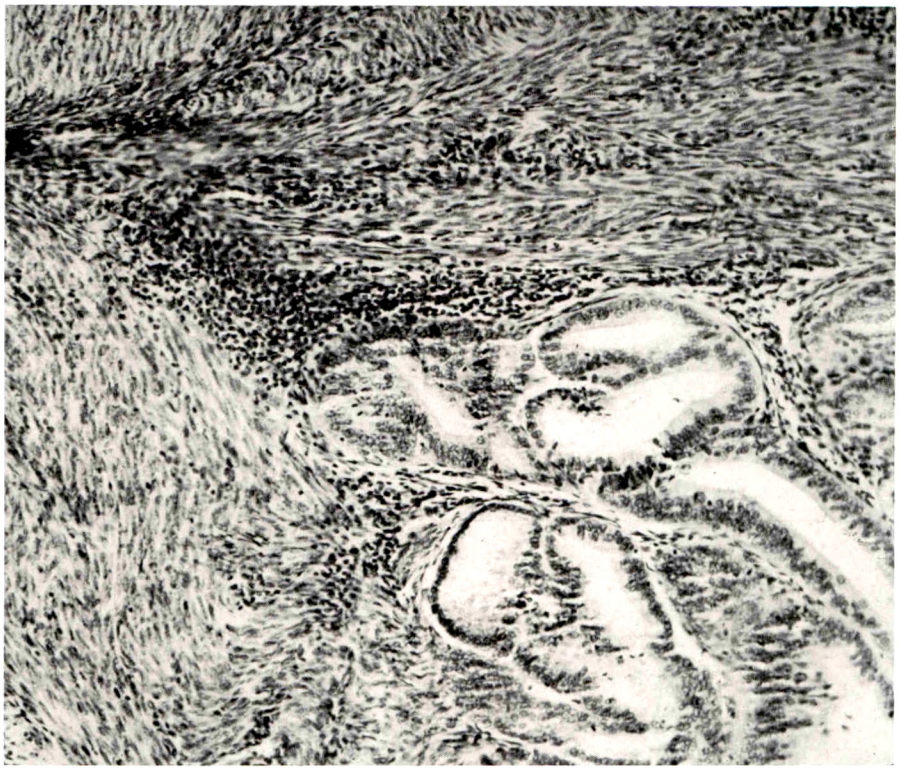


Fig. 4. Case 1. Biopsy specimen from the endometrial cavity showing the characteristics of the tumor originating within this tissue.

in which, on fractional curettage and biopsy, the lesion is found to invade the cervix. In cases of carcinoma involving the uterine body, hysterectomy is well established as the basic procedure for managing the uncomplicated operable cases. Thus, the evolution of a combined radiation and surgical approach, each to exploit its own attributes and aims in therapy, is an obvious advancement.

DISCUSSION

Adenocarcinoma of the cervix is an uncommon disease. The diagnosis was established in 35 cases, or 5.7 per cent of a total of 647 patients treated at The Tumor Institute of The Swedish Hospital for cancer of the cervix.

Differentiation of adenocarcinoma of the endocervix from that of the endometrium presented the greatest diagnostic problem.

Table I

PATIENTS WITH ADENOCARCINOMA OF THE ENDOCERVIX WHO HAD ELECTIVE POSTIRRADIATION HYSTERECTOMY

Case	Stage	Type of Hysterectomy	Endometrium	Cervix	Comment
B	I	Elective	Negative	Negative	Died after 3 years with pelvic recurrence
H	I	Elective	Negative	Negative	Living and well at 5 years
W	I	Elective	Negative	Positive	Living and well at 4 years
N	III	Elective	Negative	Negative	Died after 2½ years with pelvic recurrence
F	I	Elective	Positive	Negative	Living and well at 4 years
O	II	Elective	Negative	Positive	Terminal at 2 years with metastases
D	I	Elective	Positive	Negative	Living and well
L	II	Elective	Positive	Positive	Died after 1 year with metastases
T	I	Elective	Positive	Negative	Living and well at 7 years

TABLE II

PATIENTS WITH ADENOCARCINOMA OF THE ENDOCERVIX WHO HAD POSTIRRADIATION HYSTERECTOMY LATER FOR A SECOND DISEASE

Case	Stage	Time of Hysterectomy after Irradiation	Reason	Cancer Type and Site		Comment
				Endometrial	Endocervical	
M	II	5½ yr.	Bleeding	Positive	Negative	Died after 8 years with wide and local metastases
W	III	6 mo.	Bleeding	Positive	Negative	Died after 4 years, 9 months with local persistence
S	I	2½ yr.	Bleeding	Positive	Positive	Laparotomy showed peritoneal implants. Died after 1½ years
V	II	2 yr.	Bleeding	Positive	Positive	Exenteration for bladder and broad ligament involvement. Died after 1 year. No autopsy

The age of the patient, the site of origin of the biopsy material and the characteristics of the cells are helpful in distinguishing the disease which is present. All too often, however, the evidence is inconclusive. Furthermore the distinct possibility of simple, simultaneous, multicentric cancers of the cervix and uterus exists.

Regardless of the cell type, when cancer is found in the cervix, the avenues of spread are similar. Irradiation offers results in the treatment of cervical cancer which are superior to those of pelvic surgery; therefore, it must be a part of any therapeutic program when carcinoma of the cervix is diagnosed.

Endometrial involvement by carcinoma, on the other hand, can often persist even after extensive radiation therapy designed for carcinoma of the cervix. The incidence reported has been as high as 72 per cent in hysterectomy specimens obtained after irradiation.[8] The value of combined radiation therapy and hysterectomy in these cases is well established.[8] Surgery alone yields a high 5-year survival rate only in the operable cases.

CONCLUSION

Combination of radiation therapy with surgery in the management of adenocarcinoma of the endocervix provides these patients with the best results obtainable in modern medical practice. Moreover, this type of approach is of definite value when there is double area involvement; also, later development of endometrial carcinomas may be prevented.

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THE INTRA-UTERINE TANDEM TECHNIQUE*

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RADIUM therapy for cancer of the uterine cervix has undergone its evolutionary phase since the early days of radiation therapy, and it is now the well established method of treatment for this disease. Various systems of radium arrangements and dosage have been developed in the radiation therapy centers of the world.[1,5] Most of these follow a similar technical pattern with radium sources placed in the cervical canal and vaginal vault. In the cervical canal, 1, 2 or 3 radium capsules are arranged as a linear source in a rubber or plastic tube to form a tandem which extends into the uterine cavity. In the vaginal vault, however, there is more variety in the design of applicators to hold radium capsules in the region of the portio vaginalis of the cervix. In previous articles,[2,3] a colpostat was described for the accurate placement of a radium capsule in each lateral fornix by means of two ovoids held firmly by rods on an adjustable pivot mechanism, and in another article[4] the isodose contours were reported for most of the geometric variations that occur in the clinical application of this colpostat with the tandem. The insertion of the colpostat is a simple technical procedure that can be done in a properly equipped gynecologic examining room, for there is rarely the need for any form of anesthesia. The insertion of the rubber or plastic tandem, however, requires adequate dilatation of the cervix and must therefore be performed in the operating room, usually with general anesthesia.

Prior to the dilatation of the cervix, a uterine sound is inserted to determine the direction and size of the uterine cavity. The idea occurred to the author that, since this sound must be inserted into the uterine cavity before the dilatation is begun, the whole procedure could be greatly simplified if this sound or a similar instrument also contained the radium. The radium would then be in proper position in the uterus and no further operative procedure would be required. In this manner the intra-uterine tandem technique would be practically equivalent to the passage of the uterine sound. Such an instrument was designed, and its construction and its advantages are the subject of this paper.

DESCRIPTION OF TANDEM AND INTRODUCER

The new tandem when held by its introducer (Fig. 1) resembles the ordinary uterine sound. The tandem itself (Fig. 2) is a straight tube made of stainless steel, 3.9 mm. in its outer diameter and 0.5 mm. in its wall thickness. At one end it is smoothly rounded; at the other, it is fitted by a fine screw thread to a small flange with a projecting rod. This fine screw thread is used when the tube is loaded with radium. The inner diameter of the tube is 2.9 mm., just large enough for radium capsules of 1 mm. platinum filtration. Flat end radium capsules are the preferable type for loading in this tandem in order to approximate more closely a continuous line source of radiation. Since this tandem is used principally in the treatment of carcinoma of the cervix, it is loaded with radium in accordance with the treatment plan of the radiotherapist. The author's tandem is loaded with 40 mg. of radium, arranged in 3 capsules so that the relative strengths of 15–15–10 are in that order from rounded end to flange end, as described in previous articles.[2,4] The active length of the radium in the tandem is 6 cm. This particular length was chosen because it is suitable for the most frequently encountered size of uterine cavity

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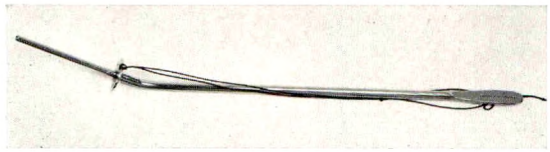


FIG. 1. Tandem held by introducer. Silk thread attached to flange.

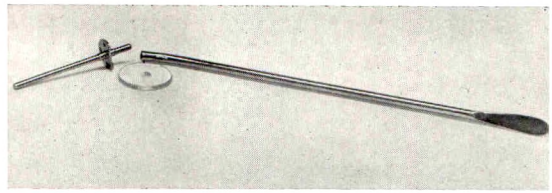


FIG. 3. Tandem, plastic flange, and introducer.

in cancer of the cervix. It is unusual to find a uterine cavity not long enough to accommodate this length tandem except for the case of cancer of the cervical stump. For the unusually small size uterine cavity or cervical stump, a shorter tandem would be required.

The flange acts as a stop against the cervix when the tandem is introduced into the uterus, but it is small enough not to obscure the view of the cervix. It is also made of stainless steel, 1 mm. thick, and it measures 2 cm. transversely and 1.5 cm. vertically. Three holes are drilled through it for attaching silk threads or sutures as needed. One heavy silk thread is attached through the middle hole to be used for handling the tandem, particularly to withdraw it from the uterus at the time it has to be removed. On one side of the flange is a small threaded projection for the threaded end of the straight tube. On the opposite side of the flange there is a solid projecting rod 1.2 cm. in length, designed to fit into the slotted end of the introducer. For those cases of carcinoma of the cervix with deep crateriform ulceration at the vaginal vault for which the flange may be too small, a clear lucite disk (Fig. 3), 3.2 cm. in diameter, can be slipped over the tandem to provide a wider stop at the vaginal vault against the ulcerated cervical lesion.

The introducer (Fig. 3) is a rod 25 cm. long with a flat handle at one end. The other end is hollow for 1.5 cm. to provide for a friction grip, and this small section of the instrument is also angulated 25 degrees to allow for the average angulation of the uterus to the axis of the vagina. The friction grip is a simple mechanism made by 4 longitudinal slots, each 1 cm. in length, in the hollow end of the instrument. This slotted end of the introducer fits over the projecting rod of the tandem and the spring-like quality of the stainless steel provides a friction grip which holds the tandem firmly but also permits easy separation of the tandem from the introducer.

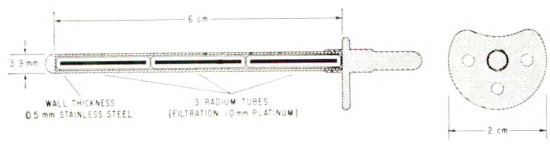


FIG. 2. Diagram showing construction of tandem with 3 radium capsules.

STERILIZATION

Because it is preferable not to subject radium to the heat of boiling or autoclaving, the tandem is sterilized cold with benzalkonium solution or a similar detergent. This method of sterilization can be done with adequate lead protection in the radium storage room, thereby avoiding radiation exposure to any of the hospital personnel. The tandem can be transported from the radium room to the treatment room in a specially constructed lead container with this solution, thereby maintaining protection for the personnel.

CLINICAL APPLICATION

The patient is prepared as for an operative perineal procedure. A preliminary sedative is administered. Anesthesia, however, is seldom required since there will be no need for dilatation of the cervix. The patient is set up as for a gynecologic examination. The cervix and vaginal vault are exposed with the aid of spades. If the uterus is mobile, the anterior lip of the cervix can be firmly held with a tenaculum. The ordinary uterine sound is then passed into the uterus to determine the direction and size

of the uterine cavity. When the sound is withdrawn, the tandem, held by the introducer, is inserted into the uterus. It is passed through the external os into the uterine cavity until the flange fits against the cervix. If the ulceration at the vaginal vault is wide and deep, the plastic flange is slipped over the tandem before it is inserted. To maintain the tandem in position with its flange against the cervix, the vaginal vault is firmly packed with gauze. During the packing procedure the introducer can be easily slipped off the tandem from which it is disengaged at the friction grip.

Roentgenograms (Fig. 4, *A* and *B*) are taken in the anteroposterior and lateral views to demonstrate the position of the tandem in the pelvis. While it is the author's treatment policy to apply the tandem first for the required treatment time and then follow it with the colpostat, it is also feasible to insert both radium applicators, tandem and colpostat, as one procedure.

After the required radium exposure time, the patient is again set up on the gynecologic examining table, the packing is removed, and the tandem withdrawn by means of the silk thread attached to one of the holes in the flange. The tandem is then placed immediately in a lead container for transport to the radium room where it is immersed in proper chemical solution for cleansing and sterilization.

CLINICAL ADVANTAGES

The most significant advantage of this stainless steel tandem is that it is narrow enough to eliminate the need for dilatation of the cervix. Theoretically, the trauma incident to dilatation of the malignant cervix may cause the spread of the neoplasm to the uterine cavity or to the parametrial lymph nodes. Also, in the friable cervix infiltrated by neoplasm, there is the

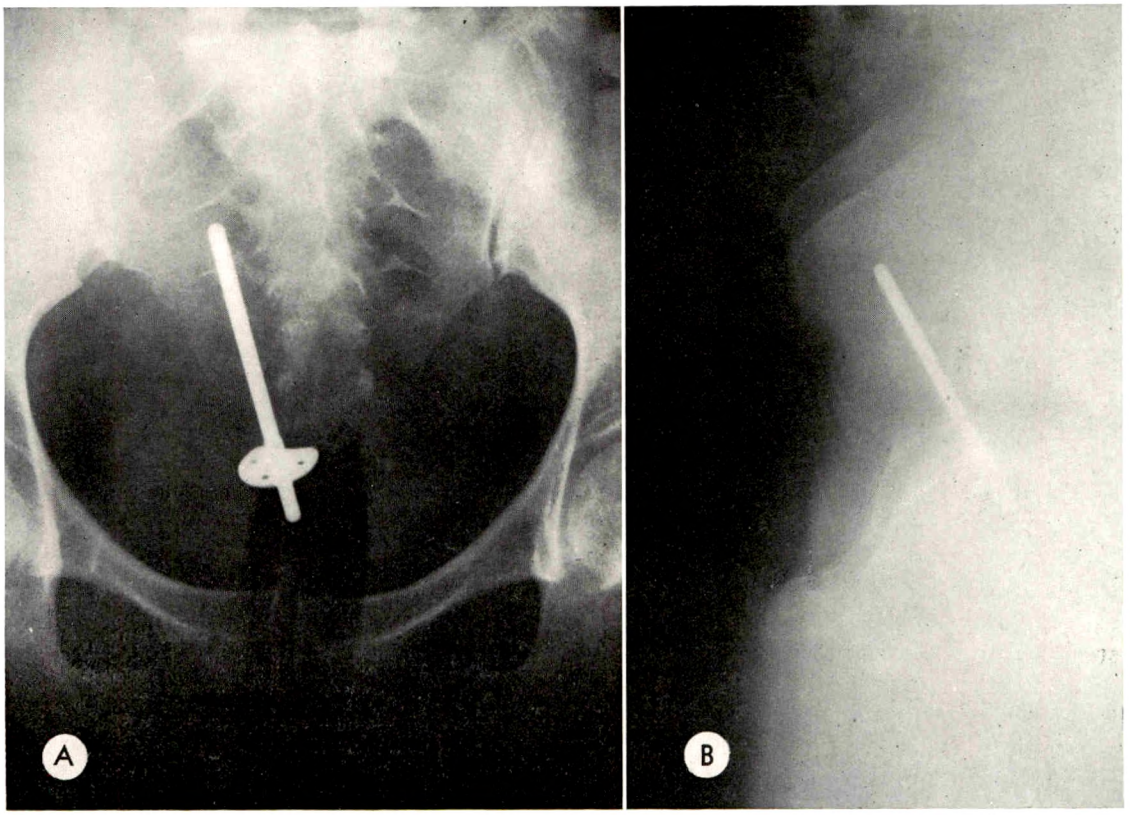


FIG. 4. (*A*) Anteroposterior and (*B*) lateral roentgenograms of the pelvis with the tandem in the uterus.

possibility of a tear with the danger of hemorrhage or perforation. Since dilatation is now no longer required, these risks are avoided. The pain that is often experienced by the patient when an instrument is introduced into the uterus is usually controlled by the preliminary sedative medication.

There is seldom need for anesthesia, either general or local, because this is usually required only for dilatation of the cervix. Therefore, the procedure of inserting the tandem into the uterus may be performed in a properly equipped gynecologic examining room instead of an operating room, provided only that the surgical rules of sterility are strictly observed, as they would be in the operating theater.

RADIATION PROTECTION

Another significant advantage of this instrument is the elimination of the radiation exposure to the radiotherapist or his technician formerly caused by the loading and unloading of the radium in the rubber or plastic tandems which had to be made separately for each patient. These could not be safely re-sterilized, and therefore a new tandem was required for each application.

It is estimated that an experienced technician with proper equipment could probably make up or dismantle a tandem in less than 3 minutes. For a 40 mg. tandem, each procedure implies an exposure of 120 mg. minutes or 2 mg. hours. The fingers are about 10 cm. away from the radium and therefore receive 150 mr. The face and head are about 35 cm. away and therefore receive about 15 mr. The chest is also about 35 cm. away but is generally protected by a lead screen 5 cm. thick so that the calculated dose is only about 1.0 mr.

Since the new tandem is made of stainless steel and its construction is simple, it can be easily cleaned in detergents and sterilized by chemical solutions repeatedly. This can be done in the radium storage room without the need for the removal of the radium. Therefore, the radium can be left in the tandem permanently, and, consequently, the radiation exposure incident to the loading and unloading of the radium sources no longer exists.

SUMMARY AND CONCLUSIONS

1. A stainless steel radium tandem together with an introducer handle is described.
2. The tandem with its introducer handle resembles a uterine sound.
3. The tandem can be inserted into the uterus with the same facility as a uterine sound. This procedure can be performed in a properly equipped gynecologic examining room.
4. Dilatation of the cervix and anesthesia are not required.
5. After the required exposure time, the packing is removed and the tandem is simply withdrawn by means of the silk thread attached to the flange.
6. The tandem can safely be re-sterilized repeatedly.
7. The radium is permanently loaded in the tandem; therefore, radiation exposure due to loading and unloading procedures is eliminated.

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I wish to express my deepest appreciation to Mr. Armando Cervi and Mr. Marc Walter of the Radium Emanation Corporation for helping me in every material and technical way to develop an idea into a practical reality.

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USE OF THE ROTTERDAM RADIUM RECONSTRUCTION DEVICE*

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IN 1953, at the Seventh International Congress of Radiology in Copenhagen, a motion-picture, "Catching the Shadows," was presented showing a method of spatial reconstruction of radium arrangement and calculation of dose. The reconstruction apparatus had been devised by Mr. J. Kaalen, engineered by Mr. Hussman, and applied clinically by Dr. Klaas Bruer, all of the Rotterdam Radium Institute. Since its inception, the technique has been widely accepted throughout the Netherlands. In the United States, the University of California, San Francisco, is the first known to have used it.

PRINCIPLES

Two roentgen beams with their central rays separated 90 degrees, and roentgen film placed perpendicularly to them, will produce two roentgenographic images of a radium needle. These two roentgenographic images lie in planes at right angles to each other. By replacing the roentgen beams with two light beams and by duplicating the geometric conditions of the roentgenographic technique, the roentgenographic images may be duplicated by shadows of dummy needles of the same dimensions as the roentgenographed needle. With these principles applied, a model can be constructed that is identical to the implant in dimension and position.

APPARATUS

The apparatus, constructed to ensure duplication of the roentgen beams by the light beams, consists of the following parts:

1. A jig (Fig. 1) which will (a) enable alignment of the roentgenographic tube and cassette; (b) ensure that the two roentgenograms are precisely at 90 degrees to each other; (c) provide a cassette holder which is rapidly changed between exposures while ensuring immobility of the patient; and (d) provide lead reference marks which will facilitate the accurate placement of the roentgenograms.

2. Dummy needles, identically constructed in length and diameter to the actual needles, on which the active ends are clearly marked. They are hinged to a wire support for easy maneuverability.

3. Light sources and film stands attached to a second jig (Fig. 2) which is used for the reconstruction of the implant. Two small light sources duplicate the positions of the roentgenographic focal spot. Two holders for the roentgenograms duplicate the positions of the films in which they were held during roentgenography. The two light beams cross just above a central platform on which the reconstruction is built.

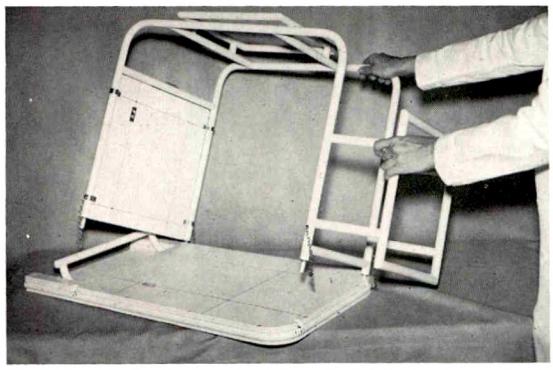


FIG. 1. Jig showing cassette holders and roentgenographic tube support.

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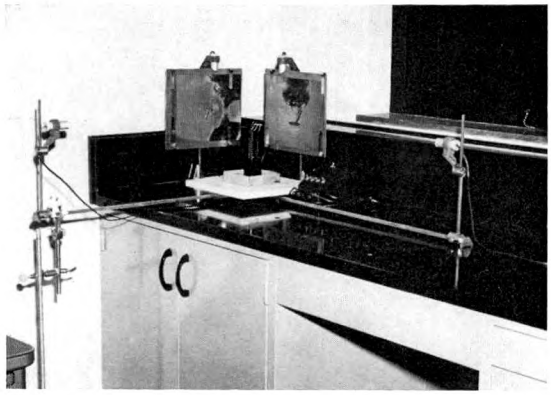


FIG. 2. Apparatus showing implant model under construction.

METHOD

The patient is positioned so that the implanted area is centered in the jig. Two roentgenograms are made at 90 degrees (Fig. 3 and 4). In order to enhance the contrast, contact prints are made. These prints show the needles in sharp detail as well as the corner reference dots (Fig. 5). A barbed point in the center of the print-stand permits each print to be impaled at the exact central axis of the beam. The reference dots enable true horizontal and vertical alignment of the prints. Movable clamps further secure them.

The light beams and reference dots are then properly aligned. Ordinary modeling clay is confined in a metal shell (such as a baby-food tin with top and bottom removed) which later forms the base. The wire support of the dummy needle is pushed into the modeling clay to stabilize it vertically. By moving the dummy needle about its hinge, it may be so positioned that its shadow coincides exactly with the image in the roentgenogram (Fig. 5). Proficiency is soon developed in adjusting the dummy needles so that their shadows superimpose the roentgenographic images.

Once the dummy needles are satisfactorily aligned, each needle hinge is soldered, sand is placed over the clay, and molten tar poured over the sand to immobilize the supports. The model is then removed from the clay base, the wire-support ends trimmed, and plaster of Paris placed in the space remaining in the metal base, thus creating a permanent model (Fig. 6).

DOSAGE CALCULATIONS

The dose to the treated volume is estimated by the Paterson-Parker system. For points of special interest, such as "hot" or "cold" spots within the implant, the contribution in dose from each needle may be readily determined by the following method.

It may be assumed that for the source-lengths generally encountered, the isodoses surrounding the radium needle may be approximated by a family of ellipses (Fig. 7). These ellipses have their foci at the active ends of the needle. As can be seen in

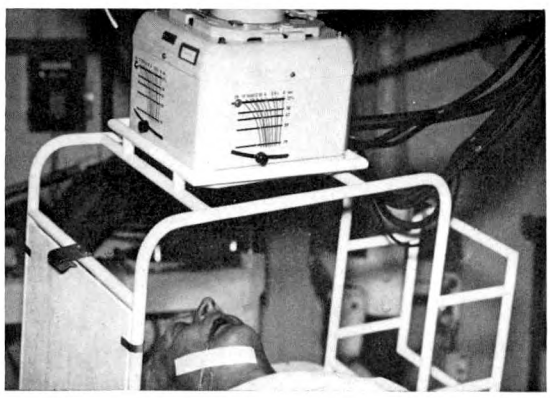


FIG. 3. Patient in jig for anteroposterior roentgenogram.

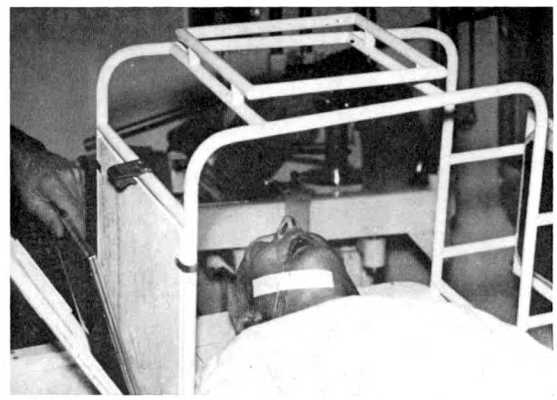


FIG. 4. Patient in jig for lateral roentgenogram.

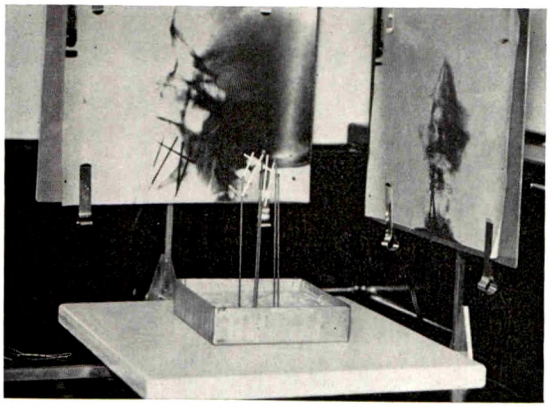


FIG. 5. Close-up view of implant model under construction showing dummy needle supports embedded in modeling clay base.

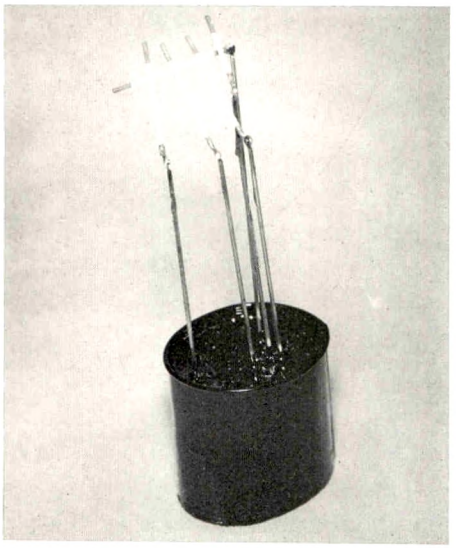


FIG. 6. Completed model of radium needle implant. White portion of needles denotes active length.

Figure 7, the ellipse does not follow the irregularity in the isodose at the ends of the needle. The precise shape of the isodose at the ends will vary, depending on the design of the needle and whether the tip or eye-end is being considered. Generally, points of interest lie within the implant volume; hence, this uncertainty at the ends of the needles is of little practical importance.

It is the nature of an ellipse that the distance a from one focus to any point on the curve plus the distance b from other focus to the same point is constant $(a+b=L)$ (Fig. 7).[1] A graph may be constructed (Fig. 8) giving the r/mg. hr. versus L for a needle of the active length used.

In practice, the determination of dose rate at any point of interest is resolved by the measurement of L from the model; *i.e.*, the sum of the distances from each active end of the needle to the point in question, and determining from the graph the corresponding r/mg. hr. for each source.

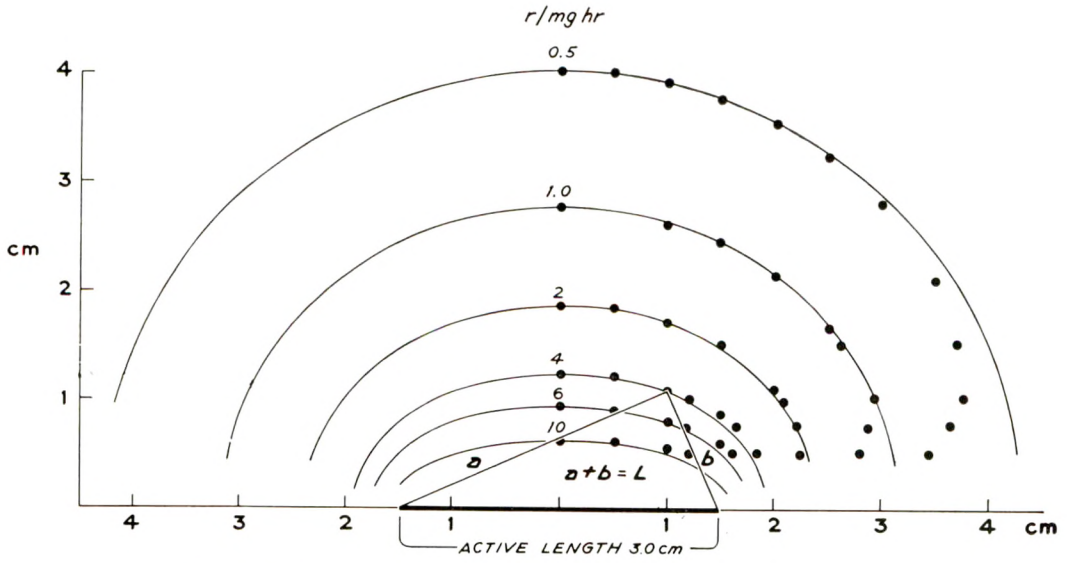


FIG. 7. Isodose curves of radium needle showing elliptical pattern.

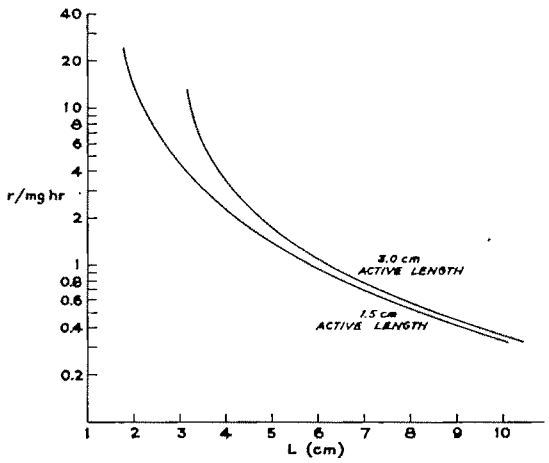


FIG. 8. Graph constructed from data in Figure 7 giving r/mg. hr. versus *L* for a needle of the active length used.

CLINICAL ADVANTAGES AND APPLICATIONS

A model of a patient's implant is a valuable aid in teaching one's self and others by actual visualization of the implant. Visualization, even with ideal roentgenograms, is difficult without such a three-dimensional aid. Accurate dosage to specific points can be quickly calculated without difficulty.

In unusual circumstances, a radium needle or needles may be removed earlier than at first planned because of overcalculated dosage, or, in low-dosed areas, the implant may require longer time.

The model may be retained as a permanent part of the patient's medical record. Differentiation of radionecrosis or recurrence in later months might be more easily re-evaluated from the reconstructed implant.

SUMMARY

A three-dimensional radium reconstruction device is described. With such a device, a permanent model of a radium implant is accurately and easily constructed. This implant model is a valuable clinical and teaching tool enabling visualization of the interstitial techniques, computation of dose to specific points, withdrawal of needles if necessary, and retention of the model as a permanent record of the implant.

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SIGNIFICANCE OF VAGINAL RECURRENCE IN ENDOMETRIAL CARCINOMA*

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THE finding of a vaginal recurrence in endometrial carcinoma seems on first encounter to be of no major concern. It is often detected on routine follow-up examinations as a small isolated nodule in the vaginal tube, usually freely movable and most often asymptomatic. Its accessibility, size and location suggest control by a variety of methods available to the radiotherapist. However, examination of our survival figures in these cases and the experience of others described in the literature indicate that vaginal recurrence is an ominous finding.

It is a well-known fact that vaginal metastasis or extension as a presenting sign in endometrial carcinoma carries a poor prognosis. The same is true of vaginal recurrence after primary treatment. The significance of this complication is that it is an indication of metastatic disease elsewhere in the pelvis. This is inferred from the poor survival rate obtained in many series despite regression of the vaginal lesion. Although examples of control of vaginal recurrences and long term survival are known, this does not apply to the majority of cases.

PRESENT STUDY

1. TYPE OF CASES

Only patients who were Stage I, Group I according to the International Classification are included in this study (Table 1). This encompasses all patients with carcinomas confined to the uterus who are clinically operable. Fifteen patients met these criteria so that a total hysterectomy and bilateral salpingo-oophorectomy was performed. Two patients who were Stage I, Group 2 (surgically operable, but medically inoperable) are not included, since the vaginal involvement was an extension of recurrence of the endometrial carcinoma in both cases and therefore a more complicated problem.

Also excluded from this study are Stage II patients, International Classification, since they present more advanced problems and would indicate the poorer prognosis. Thus, 2 patients with carcinoma of the uterus and ovary of the endometrial type are not included. In addition, those patients (5) presenting with vaginal metastases at the initial examination are not considered.

2. INCIDENCE

All patients received therapy for the vaginal recurrence in the Division of Radiotherapy and Radioisotopes, Strong Memorial Hospital, University of Rochester Medical Center, from 1927 to the present time. During this period there were 383 patients who had had primary treatment for endometrial carcinoma at Strong Memorial Hospital. Of this total number, 102 were Stage I Group I, treated by surgery, and 6 had vaginal recurrences. Nine patients were treated at other hospitals for all or part of their primary treatment. Although a large percentage of outside cases referred to the University Center had vaginal metastases, this is a selected group and has little meaning as to incidence figures. Prem[9] noted a similar finding at the University of Minnesota where 14.5 per cent of the primary cases had secondary

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TABLE I

VAGINAL RECURRENCE IN ENDOMETRIAL CARCINOMA

Patient	Stage[0]	Treatment	Pathology	Myometrial Invasion	Interval	Metastatic Site			Therapy	Status	Time of Recurrence/Survival after Recurrence (yr.)
						Apex	Tube	Parametrium			
1. A.J.	I-1	T.H.S.O. + postoperative radiation*	Well differentiated adenocarcinoma	Deep	10 yr.	+	+	o	Radium tandem	D$\bar{s}$	18/8
2. M.B.	I-1	T.H.S.O.	Undifferentiated adenocarcinoma	Superficial	3 yr.	+	o	o	Contact radium + interstitial radium	A$\bar{s}$	23/20
3. M.T.	I-1	T.H.S.O.	Poorly differentiated (+) adenocarcinoma	Superficial	1- 9 yr. 2-11 yr. 3-13 yr. 4-18 yr.	+ o o +	c + + +	o o o +	Contact radium Interstitial radium Interstitial radium 1 mev. roentgen ray	D$\bar{c}$	21/11
4. M.S.D.	I-1	T.H.S.O.	Well differentiated adenocarcinoma	Superficial	2 yr.	+	+	o	Radium tandem	D$\bar{c}$	2.6/0.66
5. C.D.	I-1	T.H.S.O.	Poorly differentiated adenocarcinoma	Deep	10 mo.	+	+	+	220 kv. roentgen ray	D$\bar{c}$	2.5/1.6
6. S.S.	I-1	T.H.S.O.	Well differentiated adenocarcinoma	Deep	11 mo.	±	+	o	Radium tandem	D$\bar{c}$	1/8/0.66
7. C.B.	I-1	T.H.S.O.	Poorly differentiated (+) adenocarcinoma	Deep	1.6 yr.	o	+	o	Radium tandem	D$\bar{c}$	2.3/0.66
8. M.H.	I-1	T.H.S.O.	Moderately differentiated (+) adenocarcinoma	Deep	1.5 yr.	+	+	o	Interstitial radium	D$\bar{s}$	2.8/1.3
9. F.S.	I-1	T.H.S.O.	Adenocarcinoma and (+) acanthoma	No	3 mo.	o	+	o	Interstitial radium	D$\bar{s}$	2.0/1.6
10. H.H.	I-1	T.H.S.O.	Undifferentiated adenocarcinoma	No	10 yr.	+ o o	o + o	o o +	Radium tandem Radium tandem Co^{60} external radiation	A$\bar{c}$	12/2.0
11. F.A.	I-1	T.H.S.O.	Moderately differentiated adenocarcinoma	Deep	3 mo.	+	+	o	Radium tandem + roentgen ray	D$\bar{c}$	0.9/0.5
12. M.M.	I-1	T.H.S.O.	Moderately differentiated adenocarcinoma	Deep	13 mo.	+	o	+	Roentgen ray	D$\bar{c}$	1.3/0.3
13. F.S.	I-1	T.H.S.O.	Undifferentiated adenocarcinoma	No	6 mo.	+	+	o	Interstitial radium + 1 mev. roentgen ray	D$\bar{c}$	1.1/0.55
14. G.S.	I-1	T.H.S.O. +** preoperative radiation	Moderately differentiated adenocarcinoma	No	3 mo.	+	o	o	Radium tandem Co^{60} external radiation	A$\bar{c}$	1.6/1.0
15. H.S.	I-1	T.H.S.O. +*** preoperative radiation	Moderately differentiated adenocarcinoma	No	6 mo.	o	+	o	Radium tandem	D$\bar{c}$	1.6/1.0

T.H.S.O.—Total hysterectomy and bilateral salpingo-oophorectomy.
D—Dead.
A—Alive.
$\bar{c}$—With carcinoma.
$\bar{s}$—Without carcinoma.
*—Postoperative irradiation consisted of (1) vaginal cylinders at apex and fornices to deliver 4,800 rγ at vaginal mucosa, and (2) external radiation to 4 pelvic fields of 200 kv., 540 r in air to each field.
**—Preoperative external irradiation to 2,000 r to tumor with Co^{60} rotation. Interrupted and did not receive planned dose of 4,000 to 5,000 r.
***—Preoperative intrauterine Heyman applicator, 5,000 mg. hr.
+—Metastases were adenocanthomas.
[0]—International staging.

vaginal involvement as opposed to 29.6 per cent in cases initially treated elsewhere.

3. TIME INTERVAL OF APPEARANCE

The time of recognition of the recurrent vaginal lesion from the time of the original treatment varies from 3 months to 10 years. Most recurrences appeared during the first 3 years and accounted for approximately 70 per cent of our series. This figure is identical to Lindgren's[6] analysis. Finn[3] and Speert[11] reported that 69 per cent and 75 per cent, respectively, of vaginal metastases are discovered within 2 years of initial therapy. Of the secondary vaginal adenocarcinomas that developed after treatment of the primary lesion, according to Prem,[9] 70 per cent did so within 2 years and 90 per cent within $3\frac{1}{2}$ years. Interestingly, there are 3 individuals with late recurrences in

the present series, all at or about the 10 year interval. Late appearing vaginal lesions are recorded as a rare exception.

4. SITE OF RECURRENCE

Most of the secondary recurrences involved the apex of the vagina or the proximal portion of the tube. Noting that there are occasions in which more than one recurrence took place, there are 8 instances of apical and tube involvement, 7 of the apex alone, and 6 instances of isolated lower vaginal wall lesions. In only 3 cases was some parametrial extension noted at the time of the vaginal recurrence. Most authors have noted a high incidence of vault recurrences as compared to lesions in the distal vagina; however, Way[14] reported 13 of 14 recurrences under the urethral meatus, 1 cm. from the vaginal introitus, and Stander[12] noted that most recurrences in his series were in the anterior vaginal wall in the lower third.

FACTORS AFFECTING VAGINAL RECURRENCE

1. TYPE OF PRIMARY TREATMENT

As all of the patients were operable candidates, total hysterectomy and bilateral salpingo-oophorectomy constituted the main part of treatment. In 12 patients only surgery was done; radiation therapy was administered as part of the treatment in 3 cases. One patient received an adequate course of preoperative intracavitary radium therapy with Heyman's applicators, and one was treated by a postoperative vaginal applicator. In the third case, the therapy plan was never completed. This indicates a much higher recurrence rate for the hysterectomy alone group (5 per cent) as opposed to that group receiving some adjuvant irradiation (0.5 per cent). This is of definite significance in that there is approximately a 2 to 1 division of primary treatment of operable cases (Stage 1, Group 1) between surgery in combination with some form of radiation versus surgery alone.

The reduction in incidence of recurrences by supplementing total hysterectomy with some form of adjuvant radiation therapy has been noted by several authors. Kottmeier[5] was one of the early proponents of prophylactic vaginal radium therapy. Recently, he reported a figure of 15 per cent vaginal recurrence with hysterectomy alone as opposed to 6 per cent with postoperative irradiation. Dobbie[2] analyzed a group of cases and found that the incidence of vaginal metastases was 5 times higher in the hysterectomy alone group as compared to hysterectomy and postoperative vaginal radium group. The University of Michigan experience with preoperative external irradiation was documented by Stander[12] and only one vaginal recurrence in 103 patients was noted, an incidence of less than 1 per cent. The controversial reports are those of Prem[9] showing a similar recurrence rate with or without radiation, and of Javert and Douglas[4] who found a higher incidence in the radiation plus surgery group as compared to the surgery alone group. The most current literature on this subject is that of Rutledge, Tan, and Fletcher.[10] They showed a reduction in the vaginal metastases rate from 20 per cent in cases receiving no radiation to 1.5 per cent when intrauterine and vaginal radium was employed prior to hysterectomy.

2. DEPTH OF INVASION

There were 12 cases in this series of which reports were available of the resected uterus; 10 showed myometrial invasion, at least 7 through more than half its thickness but not to the serosa. Finn[3] noted that 9 per cent of those cases with superficial muscle invasion had recurrences in the vagina as opposed to 27 per cent of those with deep myometrial invasion.

3. EXTENT OF INVASION

In the present series only 1 case was found to have extension to the endocervix and 2 others had extension to the internal os. Prem[9] noted a high incidence of cervical extension in his series in patients

presenting with metastases (72 per cent) as well as those developing recurrences in the vagina after primary treatment (61 per cent). In addition, he called attention to an isthmic spread, which involves most of the endometrial surface but stops abruptly at the level of the internal os, and is a factor leading to a high vaginal recurrence rate.

Kottmeier emphasized the importance of extension in regard to prognosis in endometrial carcinoma by dividing these patients into 3 groups: (1) carcinoma corporis uteri, (2) carcinoma corporis uteri et endocervicis, (3) carcinoma corporis uteri et ovarii. Lindgren, reporting the experience at the Radiumhemmet, found the survival rate to be best in cases of carcinoma of the uterus (83.8 per cent 5 year survival) with a decrease in survival rate to 62.9 per cent when there was ovarian involvement and 41.1 per cent when cervical extension was present. As mentioned, 2 cases of carcinoma of the endometrium and ovary were excluded from this study since it was impossible to determine the primary site. However, one case showing a microscopic deposit or focus in the ovary was included. In our series, neither ovarian nor cervical extension was a major factor, but its importance is obvious from the data culled from the literature.

4. HISTOLOGIC TYPE

Although no grading of the adenocarcinomas was consistently attempted, the majority of the cases were moderately undifferentiated to anaplastic carcinomas. Finn[8] noted only 8 per cent vaginal recurrences in well differentiated cancers as opposed to 44 per cent in poorly differentiated adenocarcinomas, and similarly Stander[12] noted a 5 times greater recurrence rate in the anaplastic tumors.

Of particular interest are the 4 cases of adenoacanthoma in our series of vaginal recurrences. This would account for 27 per cent of the recurrent lesions, which seems to be an unusually high incidence since adenoacanthoma forms a small part of the total group of carcinomas of the corpus uteri. Interestingly, this observation has been made by other authors. Way[14] first noted this in his series. Ten per cent (6/65) of his patients with adenocarcinomas showed metastases to the vagina, whereas 53.5 per cent (8/15) of those with adenoacanthomas developed recurrences. According to Stander,[12] the incidence for adenocarcinoma and adenoacanthoma was 8 per cent (8/101) and 28 per cent (7/29), respectively. Javert and Douglas[4] noted that the rate of spread was twice as great for adenoacanthoma.

A point worthy of note is that the metastases can differ in histology. Of the 8 cases of metastasizing adenoacanthomas reported by Way,[14] 5 were of similar histology, 2 were adenocarcinomas, and 1 was pure squamous cell carcinoma. In our experience, the original lesions were moderately undifferentiated adenocarcinomas in 2 instances in the primary specimen but adenoacanthomas in their metastatic deposits. One of the autopsied cases showed only squamous cell metastatic carcinoma in various distant sites. This raises the question as to whether the squamous cell changes in adenoacanthoma are truly neoplastic changes and not simply metaplastic changes as many authors have inferred. It also suggests that this is a more aggressive type of cancer than the typical adenocarcinoma of the uterus and not an indication of a more favorable type which will run a more benign course.

FACTORS INFLUENCING PROGNOSIS

The ultimate prognosis in a particular patient is dependent upon the success of the treatment to control the vaginal recurrence and the biologic nature of the carcinoma, its presentation and evolution. The over-all survival figures for cases with vaginal recurrences and metastases are rather poor (Table II), and in our series the figure was 20 per cent (3/15) at 5 years, 2 of whom were living with cancer. Meigs,[8] in 1929, reported that 18 of 23 such patients were dead (78.2 per cent) at 5 years, yielding an average survival of 2 years after

TABLE II

VAGINAL RECURRENCE IN ENDOMETRIAL CARCINOMA
5 Year Survival Figures

	No. of Cases	Per Cent
Present Series	3/15	20
Meigs[8]	5/23	22
Way[14]	1/14	7
Javert and Douglas[4]	8/40	20
Bloedorn[1]	1/11	9
Dobbie[2]	5/17	30
Prem[9]	6/18	33
Kottmeier[5]	40/102	40.2

surgery and irradiation. The reports of Strachan[13] and Finn[3] in the thirties are discouraging despite limited follow-up. For example, Strachan reported his results in terms of $1\frac{1}{2}$ years survival with approximately two-thirds of the patients with vaginal recurrences being deceased. Way[14] did not distinguish vaginal recurrences from metastases at the original examination in a 93 per cent mortality rate in 14 cases at 5 years. The average survival rate of 14.2 months in Stander's series and 13 of 14 patients' failure to survive 5 years again stress the poor outcome with this type of recurrence. Javert and Douglas[4] noted that vaginal metastases in 40 cases resulted in an 80.5 per cent mortality in 5 years or less after the initial diagnosis. A recent communication from Bloedorn[1] is equally as grim, indicating 1 survivor in 11 patients and an average survival time of 8.5 months.

There are only 3 reports with a 30 per cent or better survival rate at 5 years following the treatment of vaginal recurrences. In 1953 Dobbie[2] noted that 5 of 17 patients were well and alive, and in 1958 Prem[9] reported a 33 per cent 5 year figure if only primary cases were considered. The best results to date are those of Kottmeier,[5] with a 5 year survival rate of 40.2 per cent in 102 cases.

1. TYPE OF TREATMENT

In most series, treatment of nodular vaginal metastases consisted of radium, either in tandem, contact, or interstitial form. No high degree of success is universally seen with one type as compared to another. Our experience is representative of that of others in that different therapies were employed in an effort to control recurrences, single or multiple. Thus, radium in a vaginal tandem was utilized 9 times, interstitial radium 7 times, contact radium twice, and external irradiation 7 times. The one long term survivor in our series, who remained free of disease 20 years after the first recurrence, had treatment on two separate occasions with a tandem and an interstitial form of radium. In those series with the best survival figures, it is interesting to note that Dobbie[2] used a vaginal tandem of radium, Prem[9] favored interstitial radium, and Kottmeier[5] a contact radium applicator and external irradiation in combination. It is safe to conclude that no one type of therapy produces longer survival once a recurrence has appeared.

Only one observer[3] suggests ultra-radical surgery for these cases, but this seems unrealistic considering the type of patient and associated geriatric and medical problems which are encountered. No increase in survival rate has been shown by this approach, and there are no other advocates of this method.

2. TIME OF VAGINAL RECURRENCE

The length of time between the primary treatment and the vaginal recurrence is an index of the biologic aggressiveness of the tumor. All patients in this series with recurrences within 2 years of hysterectomy did not survive longer than 2 years after the recurrence was detected and treated. The long term survivors in our experience have had recurrences after 3 years, and, in Table 1, it can be seen that some metastases developed as long as 9 and 10 years later. Prem[9] made a similar observation, noting a 25 per cent 5 year survival rate if the time of recurrence was under 24 months and 56 per cent if it was longer than 2 years.

3. HISTOLOGY

In our series none of the patients with an adenoacanthoma survived. There seemed to be some correlation in that the more well differentiated adenocarcinomas tended to recur at a longer interval and the patients survived longer. No attempt to specifically correlate this fact has been made by other authors.

4. LOCATION OF RECURRENCE

The location of the vaginal recurrence in our series gave no indication of a favorable prognosis. Dobbie[2] had his best results with apical lesions, whereas Prem[9] showed the prognosis to be better when the site of recurrence was the lower vagina. Of 13 patients with lower vaginal metastases, 55 per cent survived, whereas only 21 per cent of 19 patients with lesions in the upper half of the vagina survived 5 years.

DISCUSSION

The significance of vaginal recurrence or metastases is that it is a poor prognostic sign since it is an indicator or sentinel finding of deeper spread in pelvic tissues. This is implied by the poor results and limited survival rate and from a review of the patient's course after its discovery. A large percentage of these patients die with extensive infiltration of the parametrium and pelvic organs with or without distant metastases. A much smaller percentage die of distant metastases without associated pelvic involvement.

Knowledge of the mode of spread is important in formulating a logical method of treatment. This has been a subject of much concern, and most authors agree that there are 3 possible mechanisms for vaginal recurrence or metastases after hysterectomy.

1. IMPLANTATION

Originally, implantation referred to implanting of cells shed by the endometrial carcinoma during its growth. No evidence for this exists, since most lesions are submucosal and not pedunculated masses invading through mucosal lining. At present, implantation refers to seeding of neoplastic cells at the time of surgery. This would account for the occurrence of vaginal vault metastases but would not explain the appearance of deposits in the vaginal tube and lower vagina beneath the meatal orifice.

2. LYMPHATIC SPREAD

Retrograde spread via the rich network of lymphatics is feasible and could account for lower vaginal lesions by retrograde flow of cells. This is also related to the observation that endometrial carcinomas involving the endocervix or isthmus yield a higher recurrence rate in that cervical lymphatics are involved.[9] Javert and Douglas have noted that 28 per cent of all cases of endometrial carcinomas have positive hypogastric lymph nodes on admission, and this carries a poor prognosis.

3. VENOUS SPREAD

Way[14] favors venous spread rather than lymphatic invasion as a mechanism of vaginal metastases since: (1) vaginal metastases are rare in carcinoma of the cervix, which notoriously spread via the lymphatics; (2) often other blood borne deposits are found; and (3) other blood stream metastases seed in the vaginal wall. Of these arguments, the most convincing is the last point, in view of the observation that choriocarcinoma of the uterus and hypernephroma are the only 2 other tumors that do this with any frequency. Martzloff and Manlove[7] reported that the left kidney (in 20 out of 22 instances) rather than the right was the source of spread to the vagina, probably by way of the direct connection between the renal and ovarian vein on this side.

As in most circumstances, no one answer resolves the problem of metastatic spread; rather, all 3 are contributing factors. The important point is that all mechanisms allow for possible deeper spread either by seeding along the suture line extending to the parametrium, or by retrograde lymphat-

ic flow of vascular spread in and about other pelvic viscera.

A. RECOMMENDATIONS REGARDING TREATMENT OF VAGINAL RECURRENCES

A course of extensive and intensive irradiation is advised once a vaginal metastatic lesion is detected following hysterectomy. The rationale for this radical approach is based upon the observations that: (1) vaginal recurrences are indicators of deep pelvic spread; (2) survival figures to date remain generally poor; and (3) local control achieved by radium applications does not result in long term survival.

Pertaining to the last point, which is the most crucial in the technique to be advocated, Meigs[8] noted that 10 of 16 cases of recurrences responded to local radium therapy with disappearance of the growth, but only 5 patients survived. Despite local control of 7 of 15 cases reported by Stander, only 1 patient survived 5 years and the others died of pelvic spread and/or distant metastases.

TECHNIQUE ADVOCATED

Treatment in isolated nodular vaginal metastates, independent of size, is to include the entire pelvis as well as the whole remaining vaginal tube in the field of radiation. A combined approach of internal and external irradiation is advised.

1. Internal irradiation consists of a vaginal applicator, individually suited to the patient, machined out of lucite. A T-shaped arrangement of the radium tubes is advised in the tandem (Fig. 1). A number of practical points are mentioned:

a. To obtain uniform dosage throughout the vaginal tube with some ballooning of the isodose curve in the area of recurrence, differential loadings are required.

b. Some ballooning of the isodose curves is shown in Figure 2 at the apex or proximal vagina. This is the most common arrangement used, but can be obtained in the lower vagina as well.

c. Fractionation of the radium therapy in 2,000 r to 3,000 r increments applied weekly can be done to allow for tumor regression and better tumor doses as growth flattens. Depth doses are inadequate to treat lesion in one seance.

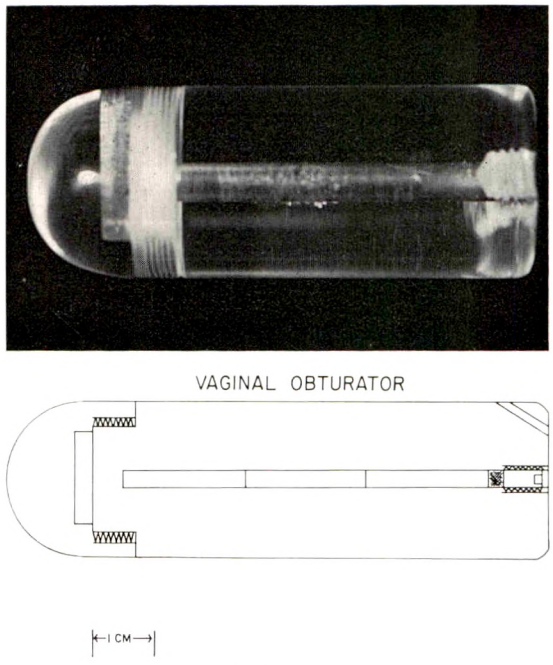


Fig. 1. Vaginal obturator.

d. A last application can be done with only one source so as to increase the dose to the recurrence site which can be identified with silver clips.

e. Ideally, the average daily dose is 1,000 r, and a maximum dose at some points, such as the apex, may be as high as 1,000 r in 12 hours. If these dose rates are maintained, bowel and bladder reactions are minimal.

f. Satisfactory results are obtained with depth doses of 6,000 r in 1 to 3 weeks with maximal values of 9,000 r at the surface of the vaginal septum.

g. No anesthesia is required; the applicator can be inserted in the bed with prior lubrication. It is held in place by a T binder. Catheterization is always done.

2. External irradiation follows the completion of the radium applications. For isolated lesions a midline shield, 2 cm. in width, over the site of vaginal application is advised to avoid excessive doses to the

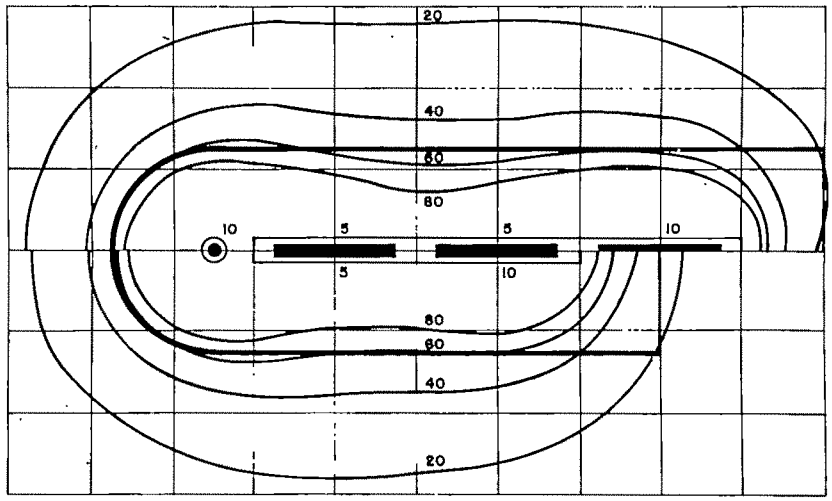


FIG. 2. Vaginal obturator with radium loadings and isodose curves. Tube loadings in mg. Ra; filtration 0.5 mm. Pt; dose rates in r per hour.

Dimensions of standard applicators

Diameter (cm.)	Length (cm.) Longitudinal Sources	
	2	3
2.0	6.5	8.5
2.5	6.75	8.75
3.0	7.0	9.0

Surface Dose Rates

Loading (mg. Ra.)	[10 + 5 + 10]			[10 + [5+5] + 10]		
Diameter (cm.)	2.0	2.5	3.0	2.0	2.5	3.0
Hours/1,000+	11.75	16.1	20.2	13.1	17.4	21.8
Maximum Dose (+)	1,170	1,090	1,070	1,260	1,220	1,145
Minimum Dose (+)	880	950	975	830	890	915

Filtration: 0.5 mm. Pt

midline. In vault lesions with parametrial invasion, the treatment plan should balance both the internal application and external irradiation so that total combined doses do not exceed 10,000 r to the vaginal surface. Total doses to the pelvic walls should reach 5,000 r depending on the tolerance and the response of the vaginal lesion. Supervoltage is usually preferable to orthovoltage in view of the obesity which is commonly present.

The aforementioned combined approach to the problem is more aggressive than Kottmeier's[5] whose last communication is as follows:

"We believe, and we think we can prove it, that vaginal metastases have always taken a much larger area of the vagina than you would actually feel or see at examination. We, therefore, stress the treatment of a much larger area. Let me take an example to explain the technique: In a case of a vaginal metastasis near the urethra, the size of a pea, we will apply radium towards this area and the surrounding tissue. The size of the applicator is about $3\frac{1}{2} \times 4$ cm., and we give a dose of at least 3,000 r 1 cm. be-

low the surface of the vagina. In addition to this treatment kilo-curie cobalt or teleradium is given towards the vulva over one portal covering the whole vulva. A dose of 2,800 to 3,000 r is given to the skin by this external radiation therapy. The interval between the local application of radium and the administration of the external irradiation is about three weeks. The external irradiation is given at 60 cm. distance during ten days. This therapy has given a five-year survival rate of 40.2% in 102 cases. The corrected survival is 41.0%."

B. RECOMMENDATIONS REGARDING PROPHYLACTIC TREATMENT

From an examination of the literature, it is noted that much controversy exists as to whether irradiation combined with surgery, rather than surgery alone, increases the length of survival. As in cases of malignancies in many other sites no truly randomized series has been reported to help settle the issue. Although this is not the subject of the present paper, our findings show that with the use of prophylactic irradiation vaginal recurrences are definitely lowered. The data to validate this fact were presented earlier in this paper, and the important consideration is whether to use radiation therapy routinely or in selected cases, and what type of application to employ.

TECHNIQUE ADVOCATED

1. Routine prophylactic irradiation is advised since it damages the tumor cells, alters the vascular bed to reduce takes, and obliterates potential lymphatic and vascular channels. A combined approach employing both external and internal irradiation is again advocated. To date, the morbidity with these techniques has been minimal.

a. External radiation is given preoperatively and consists of a 15×15 cm. field using supervoltage therapy to deliver a tumor dose of 5,000 r uniformly to the pelvis and uterus. Lampe, however, has successfully used orthovoltage irradiation with lower depth doses and has a high 5 year survival rate of 88 per cent and only a 1 per cent incidence of vaginal metastases in 103 cases thus handled. Total hysterectomy follows in 4 to 6 weeks.

b. Internal irradiation in the form of a lucite cylinder is applied to the vaginal stump postoperatively when healing is complete. This is usually done 3 weeks after surgery, and a dose of 3,000 r to 4,000 r is generally given in one seance to the vaginal surface. If the patient is uncomfortable, the procedure is divided into two applications a week apart.

2. Selected cases. If the philosophy of the gynecologist is against routine irradiation, selection of patients who are high risk candidates for postoperative irradiation is advisable. Patients with the following lesions should benefit from a prophylactic course of therapy: (a) myometrial invasion, particularly if it extends halfway or more through the wall of the uterus; (b) extension to the endocervix or isthmus of the uterus; and (c) undifferentiated adenocarcinomas and adenoacanthomas.

The technique advised in these instances is to apply a vaginal tandem postoperatively with a T-shaped arrangement of radium as previously discussed. Although this can be administered in one seance, two fractions are preferred to deliver a surface dose of 6,000 r in 2 weeks. External irradiation is added if the lesion extends to the serosa, the uterus is ruptured, or the tumor is cut across the microscopic deposits in the ovary and/or pelvic lymph nodes are found.

SUMMARY

1. An isolated vaginal recurrence in endometrial carcinoma cases carries an extremely poor prognosis. Only 1 of 15 patients is a long term survivor free of cancer in this series.

2. Fifteen cases are analyzed as to incidence, time interval of appearance, and site of recurrence.

3. The type of primary treatment was a significant factor in determining vaginal recurrences, since the recurrence rate was 10 times higher in the hysterectomy group alone (5 per cent) as compared to those

receiving some form of adjuvant radiation (0.05 per cent).

4. The extent and depth of invasion determined recurrences.

5. An interesting histologic feature is the significantly high incidence of vaginal metastases in adenoacanthoma.

6. Prognosis and survival correlated best with the time of vaginal recurrence after surgery. Those patients who developed this complication before 2 years did not survive more than 2 years.

7. Recommendations regarding treatment of vaginal recurrences are detailed. Intensive and extensive irradiation is required despite the small size and isolated nature of the lesion.

8. Prophylactic irradiation is advised routinely, but in those centers not advocating this policy a selected high risk group is defined for postoperative radium tandems.

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A COMPARISON OF TECHNIQUES FOR PARAMETRIAL IRRADIATION USING COBALT 60*

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PARAMETRIAL irradiation is almost universally accepted as essential to an adequate radiotherapeutic approach to carcinoma of the cervix. Intracavitary radium or transvaginal irradiation should adequately cover potential disease involving the vagina, cervix, uterus, and the immediate paracervical tissues. External irradiation (regardless of exact methodology) should extend the maximal tolerated dose laterally to include all the broad and uterosacral ligaments together with the included lymphatic pathways.

The lymph nodes occupy fairly constant areas in the following locations:

1. The obturator or principal lymph nodes may lie somewhat lateral to point B (revised Manchester method)[4] and usually quite near the midpoint of the acetabulum.

2. The hypogastric lymph nodes lie posteriorly in the sacroiliac area near the bifurcation of the common iliacs.

3. The external iliac lymph nodes usually lie higher than the principal obturator lymph nodes and anterior to the acetabulum.

4. The sacral and presacral lymph nodes are posterior and adjacent to the upper sacral vertebra.

It is therefore necessary to irradiate a relatively large area of the pelvis in order that all the potential tumor may be treated. However, if additional irradiation of the midline structures via radium is indicated, the external irradiation should avoid an overdose to the bladder and rectum. Similarly, in delivering a cancerocidal dose, the radiotherapist must consider tissue tolerance of other uninvolved structures such as the femoral necks, subcutaneous tissue, and skin.

It is the purpose of this paper to compare three cobalt 60 techniques of external irradiations with respect to (1) adequate coverage of tumor, (2) particular applications of each technique, and (3) sparing of uninvolved normal structures. These techniques will be evaluated in part on relative depth dose measurements determined by exposing a phantom containing x-ray film to the appropriate gamma ray beams of either fixed or moving fields.

The cobalt 60 therapy unit employed in this study has been described previously.[2] It is designed for horizontal rotation therapy, *i.e.*, the patient is placed horizontally on a cot and the gamma ray beam moves circumaxially about the long axis of the patient. The phantom[1] is composed of a plastic based on a synthetic isocyanate rubber and contains a natural skeleton. It is sectioned transversely into 2.5 cm. layers which are held together by means of a clamping device. The sections are held rigidly together during irradiation by nylon cords under tension. Film is loaded between successive layers with the edge taped to prevent light leakage (Fig. 1). After development, the film is read on a Macbath-Ansco densitometer, and analyzed as reported earlier.[3] The film used, namely Eastman Kodak Industrial X-ray AA, is a more sensitive form of the type employed previously.

TECHNIQUES

(a) *Opposing Fixed Ports.* Conventional parametrial irradiation implies the use of opposing orthovoltage or cobalt 60 portals. In general, a 4 cm. separation of the fields

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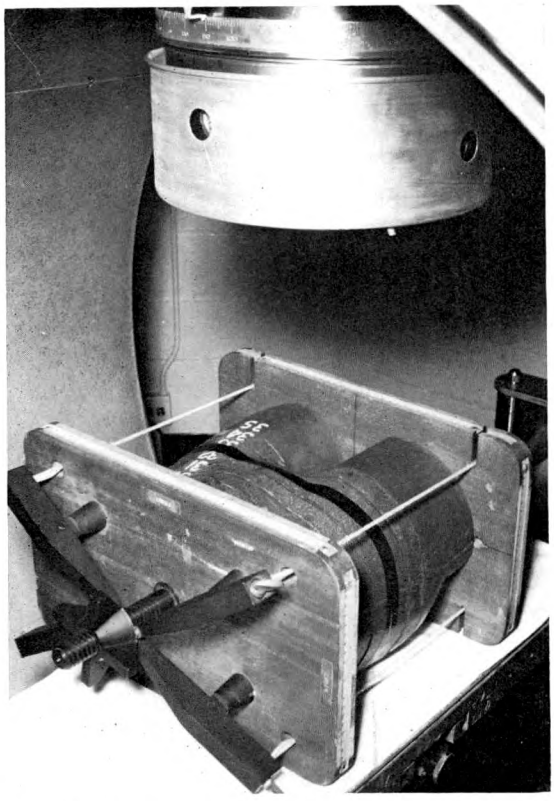


FIG. 1. Photograph showing portion of phantom (below) under cobalt 60 teletherapy apparatus. Interface of sections containing film is taped to prevent light leak. Source shield is shown on the top of the picture.

in the midpelvis is considered adequate; this may be accomplished by using one field with lead shielding in the midline, or two separate anterior and posterior fields with adequate central separation.

The dose distribution for two separate anterior and posterior fields is shown in Figure 2. The location of the pelvic bones, bladder, rectum, and vagina is indicated in the figure. An arbitrary point, C.P., is taken as the basic reference center. The points C.C. indicate the centers of crossfire. It is at the depth of these points within the phantom that the field size, namely 7×15 cm., is prescribed. The center of crossfire is at the center of each given irradiation field. In this case, the centers of crossfire are separated by 11 cm. and lie 1.8 cm. posteriorly to the reference center. The apparent lateral asymmetry of the 90° isodose lines is due to an error of ±5 per cent for the method of measurement employed, which is conspicuous here because of the low dose gradient in this region. These measurements show that the opposing fixed ports give a peak dose just below the skin surface rather than at the midpelvic line.

The simplicity of this setup is evident. Regarding dose distribution, there are several salient features:

1. The low dose (10 per cent) to femoral necks.
2. The low dose (25 per cent) to midline structures.
3. The fairly homogeneous dose in the parametrial area.
4. The higher dose to subcutaneous tissues than to the tumor (15–20 per cent greater).

(b) *Sector Techniques.* By using sector techniques, one attempts to treat the same tumor-bearing area as that treated with opposing ports, but because of the geometry, the dose distribution is considerably and beneficially different. The setup is more complex than that in opposing ports. The two sector techniques to be discussed are: (1) four sectors, each extending over 85°, with a 7×15 cm. field size at the center of rotation and (2) four sectors of 60° each, with a 5×15 cm. field size. Their relative dose distributions are shown in Figures 3 and 4, respectively. The point C.R. indicates the position of the centers of rotation in each case. These are located 11 cm. apart and 1.8 cm. posteriorly to the reference center. In these distributions, the dose maximum lies in the mid-plane of the pelvis. As usual with moving field beams, the skin dose is far lower than for the fixed-field beams. The 60° sector technique yields an elongated 80 per cent isodose line and a comparatively low dose at the immediate paracervical tissues. On the other hand, the 85° sector technique yields a more circular distribution about the centers of revolution, with a higher dose to the immediate paracervical area.

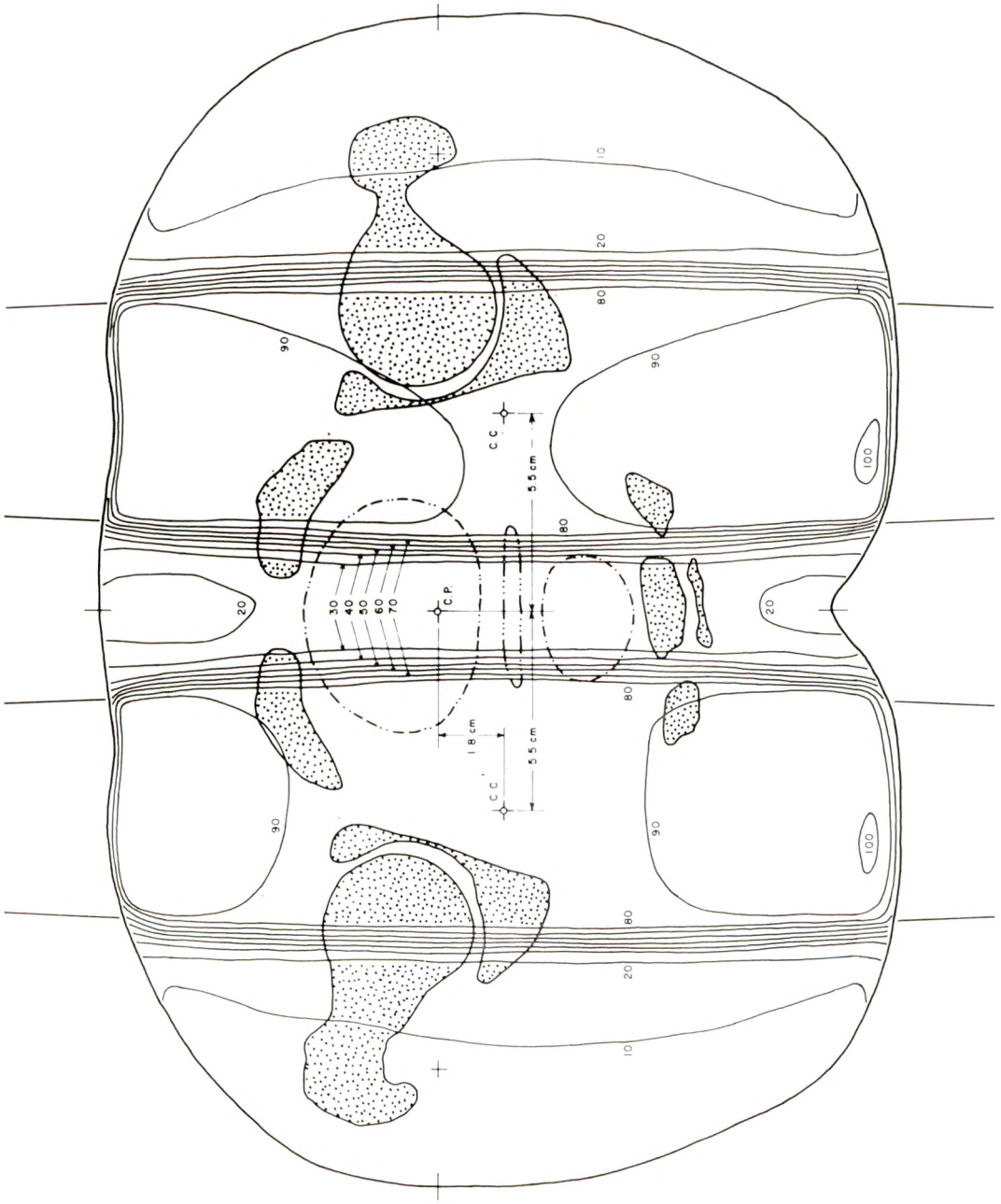


Fig. 2. Isodose distribution of cobalt 60 gamma radiation for four equal fixed fields in opposing pairs. The field size is 7×15 cm. at centers of crossfire (C.C.). The phantom is heterogeneous with the distribution measured between sections 32–33. Bone is shown in a stippled pattern. The bladder, vagina and rectum are indicated in a broken line pattern. The point C.P. is taken as the basic reference center.

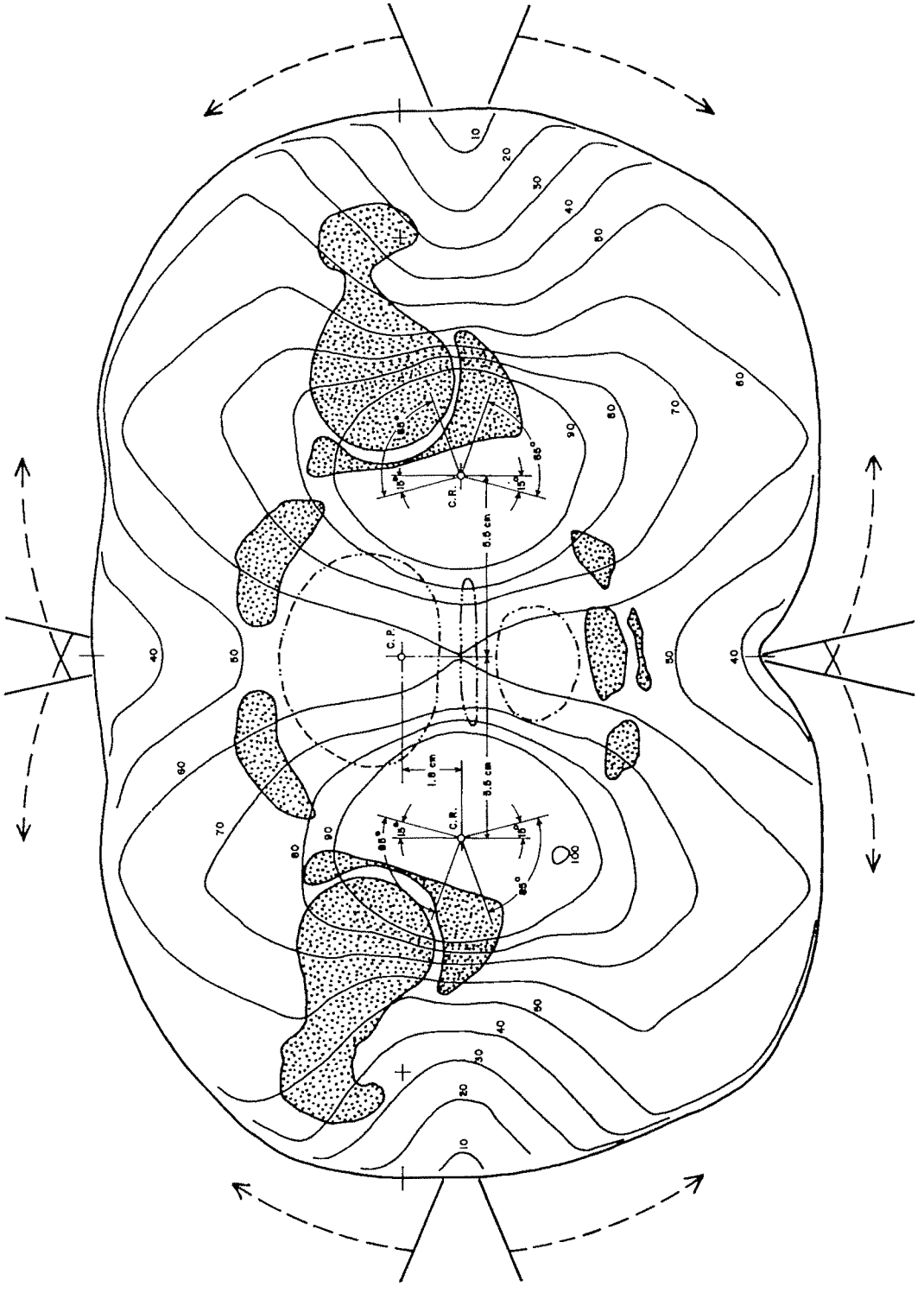


FIG. 3. Isodose distribution of cobalt 60 gamma radiation for four moving field sectors each 85°. The field size is 7×15 cm. at the centers of rotation (C.R.).

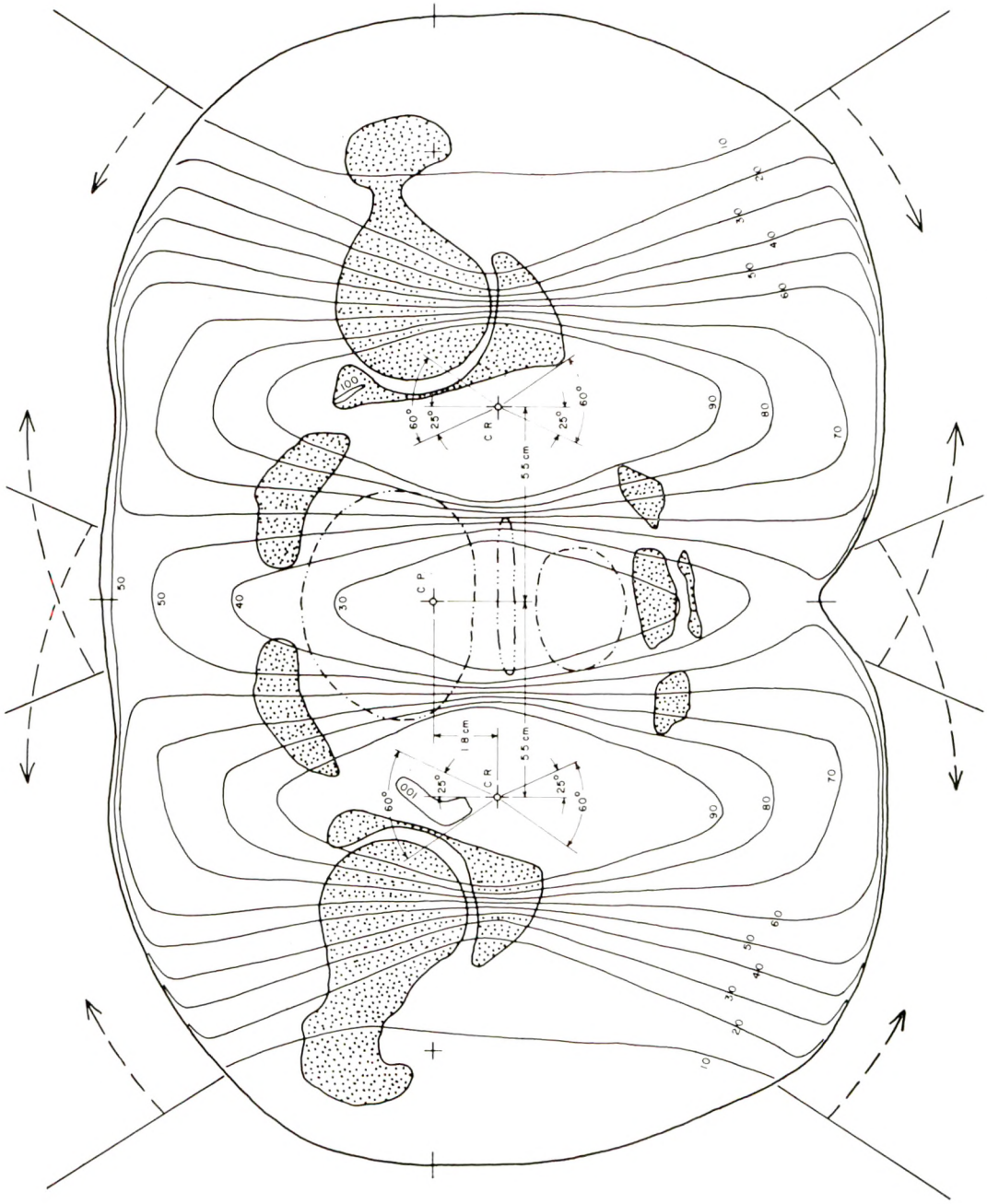


Fig. 4. Isodose distribution of cobalt 60 gamma radiation for four moving field sectors each 60°. The field size is 5×15 cm. at the centers of rotation (C.R.).

From the isodose patterns of the 60° and the 85° sectors, one notes that:

1. The femoral necks receive a low dose (10 per cent).

2. The 85° sector contributes a fairly high dose to mid-line paracervical structures (50–70 per cent), while the 60° technique gives considerably less (30–40 per cent); the opposing port technique contributes least.

3. Lymph node areas receive homogeneous doses with both techniques. The 60° sector extends the zone of effective radiation slightly more anteriorly and posteriorly than the 85° sector.

4. Subcutaneous tissues receive *less* radiation than potential tumor-bearing areas with both sector techniques.

Some estimates of integral dose, based solely on the two-dimensional distributions presented here, were made. The total integral doses with fixed-field and the 85° sector were respectively, 7 per cent and 23 per cent higher than those of the 60° sector. It should be remembered, however, that the field size is smaller with the 60° sector. Assuming the tumor to involve the previously described lymph node areas, rough estimates were also made for the ratios of tumor integral dose to total integral dose. These were 24, 26 and 22 per cent for the fixed field, 60° sector, and 85° sector cases, respectively.

DISCUSSION

Theoretically, the primary tumor site has received adequate radiation from radium or transvaginal roentgen rays, and there should be no necessity of adding to this dose with external therapy. However, many factors, such as anatomic variation, extent of tumor, and associated pelvic infection may either prevent initial radium insertion or cause a compromise in the dose distribution obtained therefrom. This being the case, split opposing ports which deliver a very low dose to the midline paracervical structures would be a poor choice for preliminary irradiation intended to improve the situation for radium insertion.

Of the two sector plans, the 60° one gives only a slightly better dose to the centrally located tumor-bearing structures than the fixed opposing ports, and would have no obvious advantage in the previously described situation. With the 85° sector, however, there is a good "blending" of dose to the midline. This technique, then, would seem to be appropriate for a situation where preliminary external treatment is given to facilitate subsequent radium therapy, and the same technique could then be continued to achieve the desired lateral pelvic dose.

Skin tolerance is not a problem in any of the three cobalt 60 techniques described, but the isodose patterns reveal that the subcutaneous tissues receive the maximum dose with split opposing fixed ports, while the tumor area receives the maximum dose with the rotational method. While this dose maximum in the subcutaneous tissues with the opposing fixed ports may be clinically insignificant if the tumor dose is kept within the usually accepted range, it is an unnecessary burden to the patient if it can be satisfactorily avoided.

A further comparison of the three techniques via "integral dose," reveals no apparent significant difference. In any event, all three approaches are clinically well tolerated by the patient.

CONCLUSION

If rotational cobalt 60 is available, there should be no real necessity to employ straight opposing ports for external irradiation to cancer of the cervix.

The 60° sector would seem indicated when the various factors for intracavitary or transvaginal irradiation are optimal and only the structures lateral to the paracervical areas need supplementary treatment.

The 85° sector should be very well suited for complicated cases in which significant pre-radium roentgen therapy to midline structures is necessary, but for which one still wishes to make use of the other advantages of the 60° sector.

Although the sector techniques have a

complex alignment procedure, the extra precautions necessary should be ultimately rewarding.

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SHORT AXIS ROTATION WITH COBALT 60 TELETHERAPY UNIT, USING COPPER WEDGE FILTERS AND SQUARE FIELDS*

PART I. DOSIMETRY

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COBALT 60 units are generally available in all parts of the world. This makes possible the use of supervoltage therapy by the small clinic. From physical considerations alone, the higher the energy of radiation available, the easier it is for the radiologist to treat a deep tumor and to spare the surrounding normal tissues. Of all the high energy radiation units used for radiation therapy today, a well designed cobalt 60 unit is superior for a small or remote clinic due to the simplicity of the technical maintenance required.

Because of the increasing availability of cobalt 60 units, it is well to investigate all the possibilities that such units can offer. The radiation dosimetry of cobalt 60 therapy has been studied quite thoroughly for routine use, employing fixed or static ports, and for long axis rotation. Very little data have been published for the use of short axis rotation with this high energy radiation.

Short axis rotation therapy, also called conical rotation and horizontal rotation, is a method of rotation treatment in which a beam of radiation (usually fixed) enters a rotating patient at an angle of less than 90° to the axis of rotation of the patient. Generally, the angle of the central ray to the axis of rotation is between 30° and 60°. The central ray, after 360° of rotation, has outlined a cone within the body of the patient. Short axis rotation can be adapted inexpensively to any cobalt 60 unit in which there is no fixed counter-weight in the beam path. By the addition of a rotating table and a method of beam localization (pin and arc), any stationary unit can be made flexible enough to include short axis rotation therapy in its armamentarium.

The data presented here were obtained by selecting a set of physical factors which appeared to us most suitable to the clinical problems. The experimental investigations were carried out with a cobalt 60 Keleket-Barnes teletherapy unit. The radioisotope sources used consisted of two different cobalt 60 sources, both having a diameter of 2 cm., but the second of greater height and intensity. This did not change the isodose pattern appreciably.

All measurements were made using a beam of radiation entering the superior horizontal surface of a rotating cubic phantom at 45° to the axis of rotation of the phantom. The distance from the source to the presenting surface of the phantom at the central ray was maintained at 70 cm. A Victoreen condenser r-meter with a 100 r chamber, Model 621 (accuracy ±5 per cent) and a cubic pressdwood phantom (30×30×30 cm.) with an average density of 1.04 were used throughout the study. The rotation table used is by Marconi. This table has a floating top and an axis-indicating plastic disc to facilitate positioning of the patient and tumor to the axis of rotation of the table. The beam localization was done using an ordinary pin and arc. Figure 1 shows the pin and arc in position to aim the radiation beam at a tumor located 5 cm. below the surface of the skin and on the axis of rotation. An angle of incidence of 45° and an average source skin distance of 70 cm. were main-

* From the Radiation Therapy Center of the Hospital of St. Raphael, New Haven, Connecticut. Supported by a grant in aid from the local division of the American Cancer Society.
Presented at the Forty-fourth Annual Meeting of the American Radium Society, New York City, April 2–4, 1962.

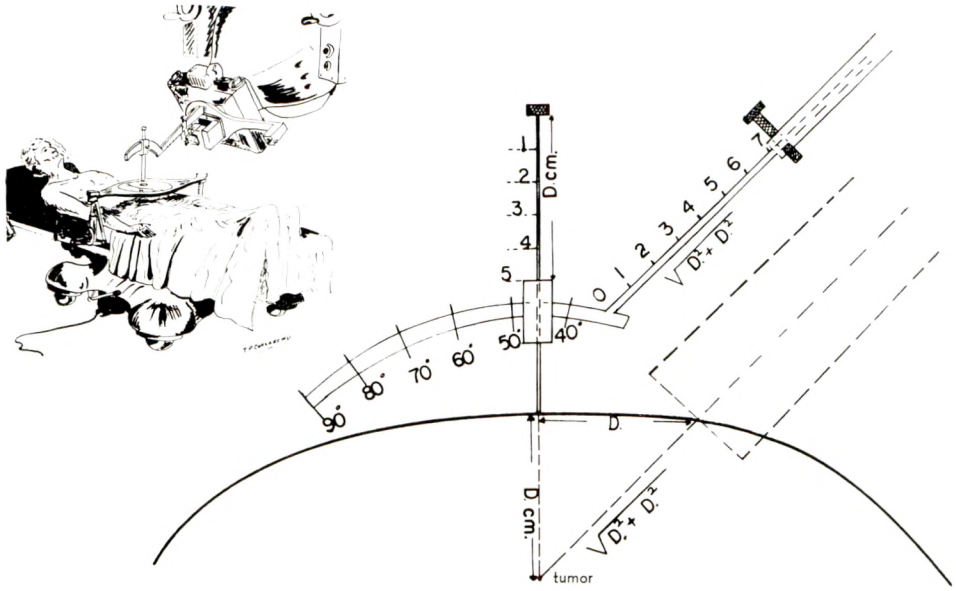


FIG. 1. Schematic drawing of the pin and arc in position to set up the cobalt 60 treatment of a tumor 5 cm. below the skin with an angle of incidence of 45° to the vertical. The insert shows the relative position of the patient, pin and arc, plastic disc localizer, and radiation unit during set-up. The plastic disc localizer and the pin and arc are removed during the actual treatment.

TABLE I

COBALT 60—SHORT AXIS ROTATION—360°—ANGLE OF INCIDENCE 45°—70 CM. S.S.D.—SQUARE FIELDS

DEPTH DOSE ALONG AXIS OF ROTATION

Area Field at Surface	Depth Along Axis of Rotation (cm.)																	
(cm.²)	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Center of Rotation at Surface																		
25	100	98	90	79	76	47	33	22	13	8	5	2						
35	100	99	91	81	78	51	36	25	15	11	7	4						
45	100	99	92	82	79	54	40	28	18	12	9	5						
55	100	99	92	83	80	59	45	32	22	14	10	6						
64	100	99	93	83	80	64	51	36	28	18	10	6						
Center of Rotation 2 cm. Below Surface																		
25	95	101	100	91	86	75	60	49	38	26	17	13	5	2				
35	100	101	100	93	86	76	60	51	41	31	24	17	10	3				
45	102	102	100	93	86	77	61	52	43	34	26	19	13	4				
55	104	102	100	94	87	77	63	53	44	35	27	20	14	5				
64	108	104	100	94	89	77	66	53	45	35	28	21	15	5				
Center of Rotation 4 cm. Below Surface																		
25	64	76	96	101	100	94	86	74	61	46	36	25	17	11	8	7		
35	81	93	102	103	100	94	86	76	65	53	43	33	26	18	12	8		
45	92	100	105	104	100	95	86	78	67	57	47	38	30	22	15	10		
55	101	105	106	104	100	95	89	80	69	59	49	39	31	24	17	14		
64	109	108	107	104	100	96	90	81	71	60	49	40	32	25	18	15		
Center of Rotation 6 cm. Below Surface																		
25	32	47	74	93	103	105	100	91	82	71	62	51	40	29	18	8		
35	41	54	82	101	110	107	100	92	82	75	66	56	46	38	30	21	15	7
45	60	73	96	110	113	108	100	92	84	78	69	60	51	43	33	24	16	8
55	83	96	110	116	115	108	100	93	84	78	71	62	54	46	36	27	18	10
64	97	106	116	118	119	109	100	93	85	78	72	62	56	46	38	30	21	14

TABLE II

COBALT 60—SHORT AXIS ROTATION—360°—ANGLE OF INCIDENCE 45°—70 CM. S.S.D.—SQUARE FIELDS

DEPTH DOSE ALONG AXIS OF ROTATION

Area Field at Surface (cm.²)	Depth Along Axis of Rotation (cm.)																				
	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Center of Rotation 8 cm. Below Surface																					
25	16	19	35	54	75	92	101	104	100	90	81	71	61	53	42	31	22	12			
35	18	23	37	54	76	94	103	104	100	91	84	75	66	57	48	39	31	20	9		
45	20	24	38	56	78	99	105	105	100	93	85	77	69	61	52	43	36	26	18	9	
55	35	38	59	78	98	109	110	106	100	94	86	78	71	62	54	46	38	29	21	13	
64	68	85	112	129	131	125	118	109	100	94	86	79	72	63	56	47	39	30	22	13	
Center of Rotation 10 cm. Below Surface																					
25	16	17	19	25	37	56	76	92	102	103	100	89	81	72	61	49	37	30	7		
35	16	18	26	35	58	68	92	105	109	107	100	92	84	75	66	55	44	33	21	9	
45	18	20	29	48	73	96	112	116	114	108	100	93	86	77	68	59	49	38	30	20	3
55	23	27	39	65	95	118	127	123	117	109	100	94	87	78	70	62	52	42	38	29	21
64	33	41	64	87	110	127	131	125	118	110	100	94	87	78	71	64	55	46	42	36	31
Center of Rotation 12 cm. Below Surface																					
25	12	13	14	16	19	28	39	54	70	88	103	104	100	92	84	73	65	58	48	41	32
35	15	16	16	19	25	35	49	67	86	103	112	108	100	93	86	78	69	60	52	42	34
45	17	17	19	23	31	50	73	93	108	114	115	109	100	94	87	80	72	63	55	48	41
55	17	18	22	27	39	61	86	109	121	118	115	109	100	94	88	81	73	66	58	51	44
64	18	19	23	32	47	68	92	114	123	120	115	109	100	94	88	81	74	67	59	53	45

tained. The sketch in Figure 1 shows the relative position of the patient, pin and arc, plastic disc localizer, and radiation unit (the localizer and pin and arc are removed during the actual treatment).

Data for isodose charts and depth dose tables indicating percentage dose along the axis of rotation were obtained using two beam arrangements.

First, the regular collimator of the standard Keleket-Barnes kilocurie unit, giving a 40 cm. distance from the face of the collimator to the point of entrance of the central ray on the surface at 70 cm. source skin distance, was used. The results of the first arrangement are shown in Figure 3*a*, where an experimentally determined isodose curve set for 360° of rotation with a 6×6 cm. field at the surface (70 cm. source skin distance) and for apex depths from 5 cm. to 10 cm. below the surface, is presented. By apex depth is meant the distance of the point of intersection of the central ray and the axis of rotation

TABLE III

COBALT 60—SHORT AXIS ROTATION—360°—70 CM. S.S.D.—SQUARE FIELDS

FACTORS TO DETERMINE r/MINUTE AT CENTER OF ROTATION*

Area Field at Surface (cm.²)	Apex Depth (cm.)						
	Surface	2	4	6	8	10	12
25	1.048	.900	.733	.594	.477	.341	.286
35	1.076	.932	.774	.600	.480	.383	.308
45	1.078	.937	.786	.611	.486	.400	.320
55	1.078	.943	.798	.628	.494	.407	.324
64	1.079	.950	.799	.637	.514	.410	.347

* The r/minute at the center of rotation is obtained by multiplying the corresponding factor above by the output at 0.5 cm. below surface for the corresponding straight field. To obtain the rad/minute multiply the r/minute by 0.97.

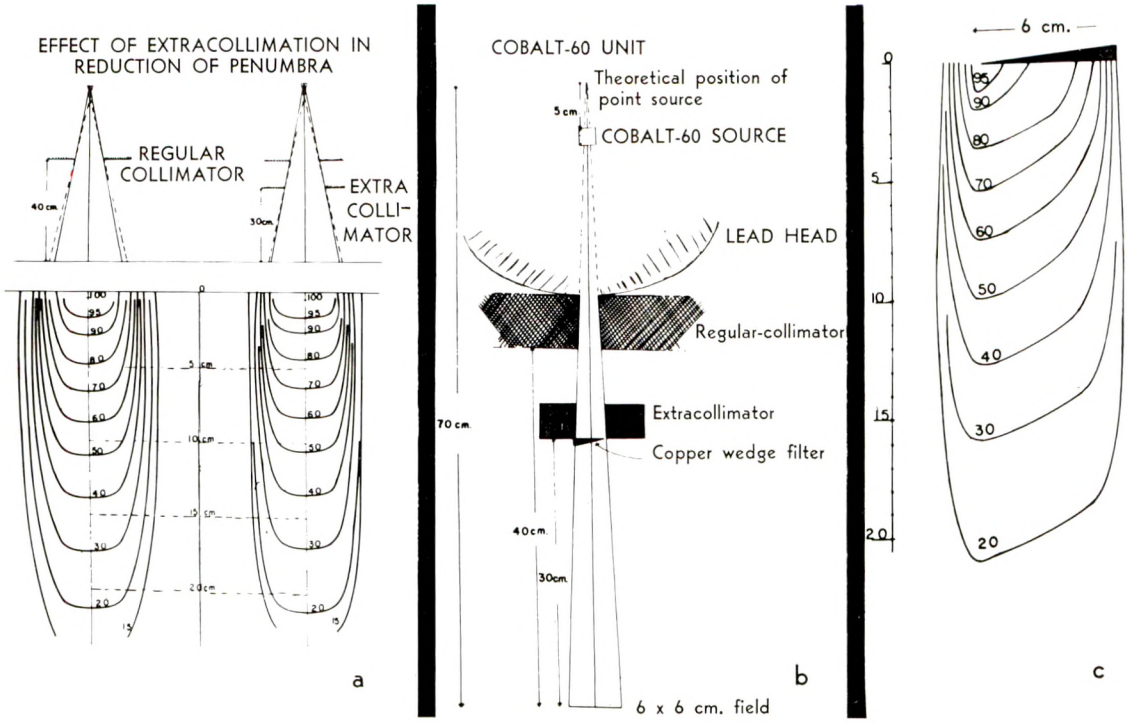


FIG. 2. Diagrams showing the effect of the addition of extracollimation and copper wedge filter to the cobalt 60 unit. (*a*) The collimator to skin distance is reduced from 40 to 30 cm. at 70 cm. source skin distance. The penumbra is reduced from 30 to 15 per cent at 1 cm. from the edge of a 6×6 cm. field at the surface. (*b*) Relative positions of the head of the kilocurie Keleket-Barnes cobalt 60 unit and the extra collimator with the copper wedge filter attached. (*c*) Sample of isodose chart for straight field obtained using extra-collimation and 16.8° wedge filter for a 6×6 cm. straight field at 70 cm. source skin distance.

below the surface of the patient or phantom along the axis of rotation. Tables I and II show a tabular arrangement of our data with measured values for depth doses along the axis of rotation for apex depths from the surface of the phantom to 12 cm. below the surface, and for field areas ranging between 25 and 64 square centimeters at 70 cm. source skin distance. In both isodose curves and depth dose tables, the dose at the apex of rotation is taken arbitrarily as 100 per cent. To facilitate the calculation of the dose at the apex, Table III listing r/minute factors was constructed. The 100 per cent dose at the apex was related to the 100 per cent dose of the identical square field for conventional cobalt 60 therapy at 0.5 cm. below the surface.

Second, the penumbra of the radiation beam was trimmed or reduced one half by the attachment of a second collimator below the regular collimator. The additional collimator consists of a set of lead blocks, each 4 cm. thick, with apertures designed according to the desired field sizes at 70 cm. source skin distance. The effect of the additional collimation is shown in Figure 2*a*: the collimator to skin distance is reduced from 40 to 30 cm. at 70 cm. source skin distance; the penumbra at the surface is reduced by about 50 per cent, and the change in shape of the measured isodose chart for a 6×6 cm. straight field is demonstrated (Fig. 2*a*).

Later, copper step wedge filters were designed to be used with the additional collimator (Fig. 2*b*). This was done in order to minimize the hot points along the axis of rotation above the apex and to produce more spherical isodoses about the apex. The best distribution was obtained with a wedge slope of 16.8° for field sizes of 7×7

TABLE IV

COBALT 60—SHORT AXIS ROTATION—360°—ANGLE OF INCIDENCE 45°—70 CM. S.S.D. COPPER WEDGE FILTER—16.8° SLOPE AND ADDITIONAL COLLIMATOR—SQUARE FIELDS

DEPTH DOSE ALONG AXIS OF ROTATION

Area Field at Surface	Depth Along Axis of Rotation (cm.)																	
(cm.²)	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Center of Rotation at Surface																		
25	100	99	97	88	57	27	3											
35	100	99	97	89	71	43	17	8										
45	100	100	98	90	80	58	33	21	6									
55	100	100	98	93	86	71	48	33	18	7								
64	100	100	99	96	92	79	62	43	27	16	8							
Center of Rotation 2 cm. Below Surface																		
25	22	37	100	94	79	59	38	30	26	3								
35	95	97	100	96	90	82	70	55	32	11								
45	99	101	100	97	93	87	80	71	59	43	22	2						
55	99	102	100	97	93	88	82	73	62	45	30	17	6					
64	99	102	100	98	94	89	84	75	62	47	33	22	11					
Center of Rotation 4 cm. Below Surface																		
25	9	13	57	85	100	94	88	75	67	56	41	30	9					
35	60	72	91	101	100	96	90	82	73	62	49	31	11					
45	93	101	106	105	100	97	91	86	76	67	54	33	14	5				
55	96	101	108	105	100	98	91	87	79	70	58	38	22	12	6			
64	99	102	108	105	100	98	92	87	81	73	62	46	35	22	18	11	5	
Center of Rotation 6 cm. Below Surface																		
25	3	5	10	33	52	72	100	94	87	76	48	33	12					
35	35	39	73	97	104	103	100	95	88	79	65	51	33	22	5			
45	48	50	96	108	108	105	100	96	89	82	75	65	54	38	20	9		
55	64	68	103	112	109	105	100	96	90	84	78	69	59	47	32	21	11	
64	95	101	107	114	109	105	100	96	92	87	80	72	62	50	40	30	22	14

cm. or less at the surface and a 25.5° slope for fields of 8×8 to 10×10 cm. at the surface. With both wedges a gap and plateau of 2 mm. were left at the collimator margins. An isodose chart for a straight field of 6×6 cm. at the surface, using the 16.8° slope copper wedge filter, is shown in Figure 2*c*. The wedge filters were designed with a constant value of slope. For each of the field sizes used, the length of the wedge,

TABLE V

COBALT 60—SHORT AXIS ROTATION—360°—ANGLE OF INCIDENCE 45°—70 CM. S.S.D. COPPER WEDGE FILTER—16.8° SLOPE AND ADDITIONAL COLLIMATOR—SQUARE FIELDS

DEPTH DOSE ALONG AXIS OF ROTATION

Area Field at Surface	Depth Along Axis of Rotation (cm.)																			
(cm.²)	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Center of Rotation 8 cm. Below Surface																				
25	2	4	9	17	30	62	88	96	100	95	85	76	62	52	33	17				
35	12	19	26	72	91	99	102	103	100	95	88	80	72	62	45	31	15			
45	20	28	50	93	100	105	107	107	100	96	90	83	78	67	52	39	24	13		
55	37	46	72	101	107	113	110	108	100	96	91	85	79	70	56	45	33	23	11	
64	78	91	109	113	116	113	110	109	100	96	91	86	80	71	58	49	40	30	18	
Center of Rotation 10 cm. Below Surface																				
25		3	8	15	28	49	79	94	100	97	100	94	84	65	40	23				
35	10	11	15	25	38	70	94	103	107	102	100	95	88	82	74	64	54	38	15	3
45	16	16	21	37	53	90	107	109	109	104	100	95	89	84	76	66	59	43	24	4
55	24	30	42	64	81	106	113	111	110	106	100	95	90	84	76	67	60	44	31	5
64	38	56	83	108	119	120	118	115	111	106	100	95	90	84	76	67	60	46	34	7

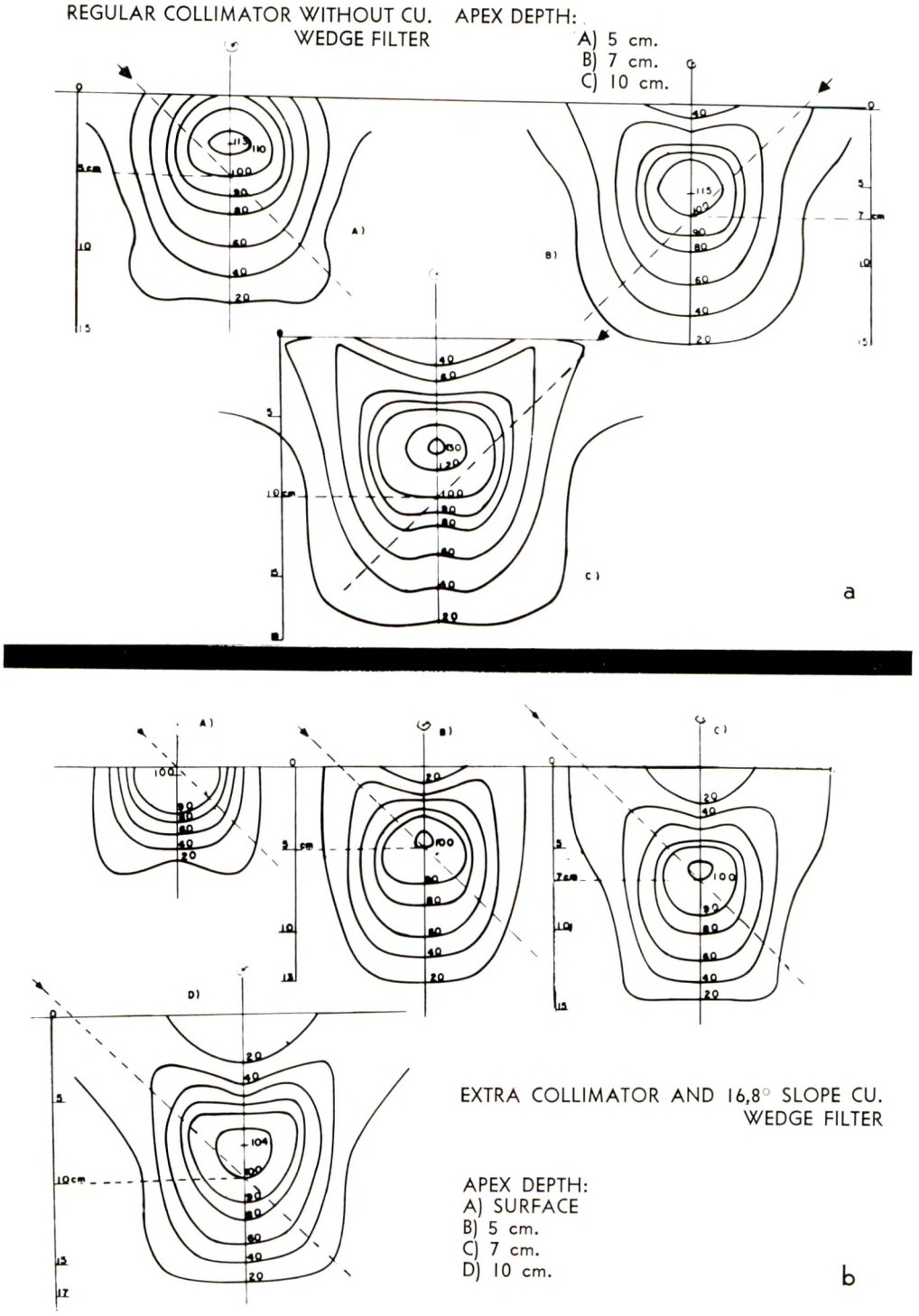


FIG. 3. Experimentally determined isodose charts for cobalt 60 short axis rotation (360°), angle of incidence 45°, 70 cm. source skin distance, using: (*a*) 6×6 cm. field at the surface, the regular collimator without copper wedge filter, and apex depths of A) 5, B) 7 and C) 10 cm.; (*b*) 5.5×5.5 cm. field at the surface, regular plus extracollimation with the 16.8 degree slope copper wedge filter, and apex depths of A) 0, B) 5, C) 7 and D) 10 cm.

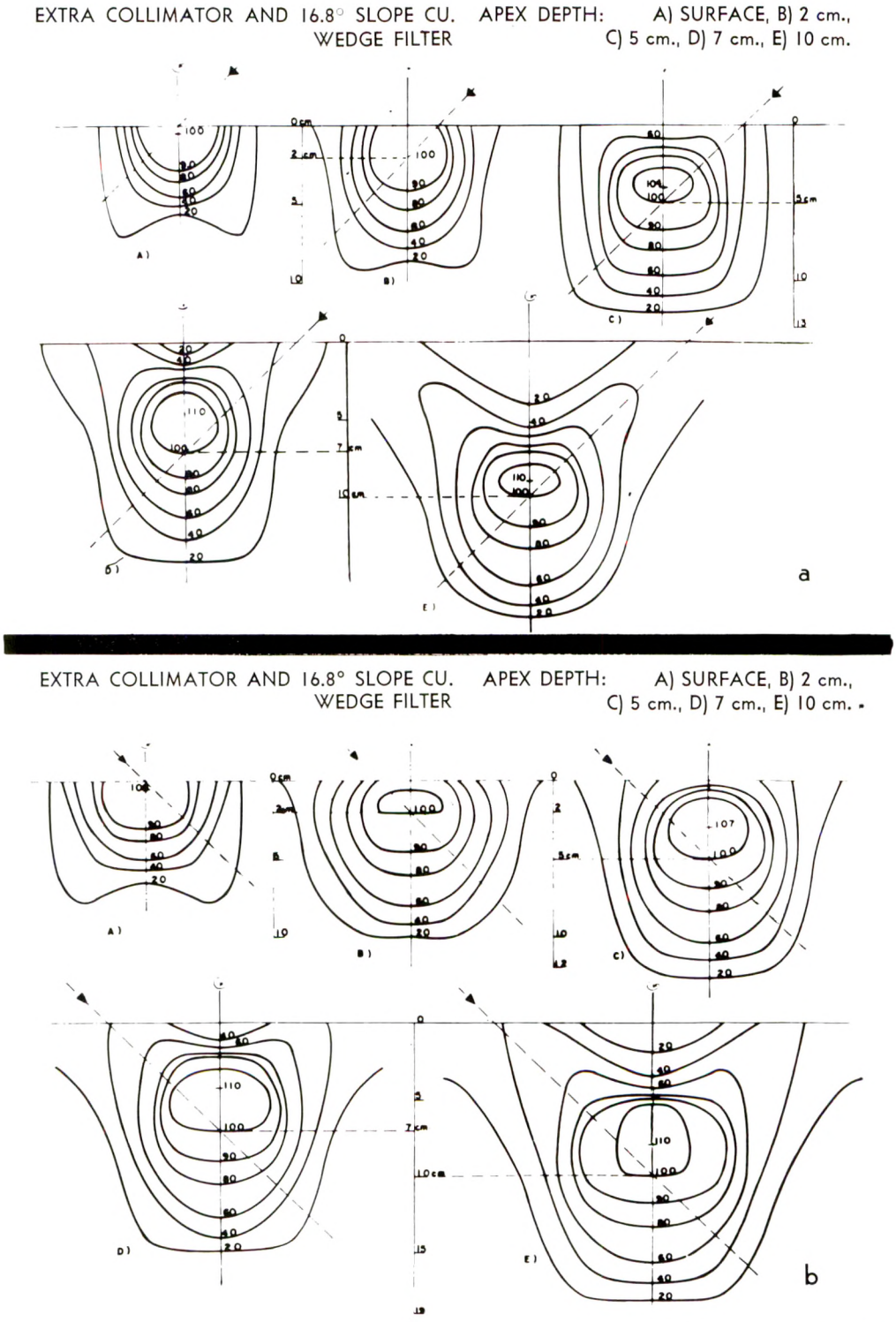


FIG. 4. Experimentally determined isodose charts for cobalt 60 short axis rotation (360°), angle of incidence 45°, 70 cm. source skin distance, using extracollimation and 16.8° slope copper wedge filter for (*a*) 6×6 cm. field at the surface and apex depths of A) 0, B) 2, C) 5, D) 7 and E) 10 cm.; (*b*) 6.7×6.7 cm. field at the surface and apex depths of A) 0, B) 2, C) 5, D) 7 and E) 10 cm.

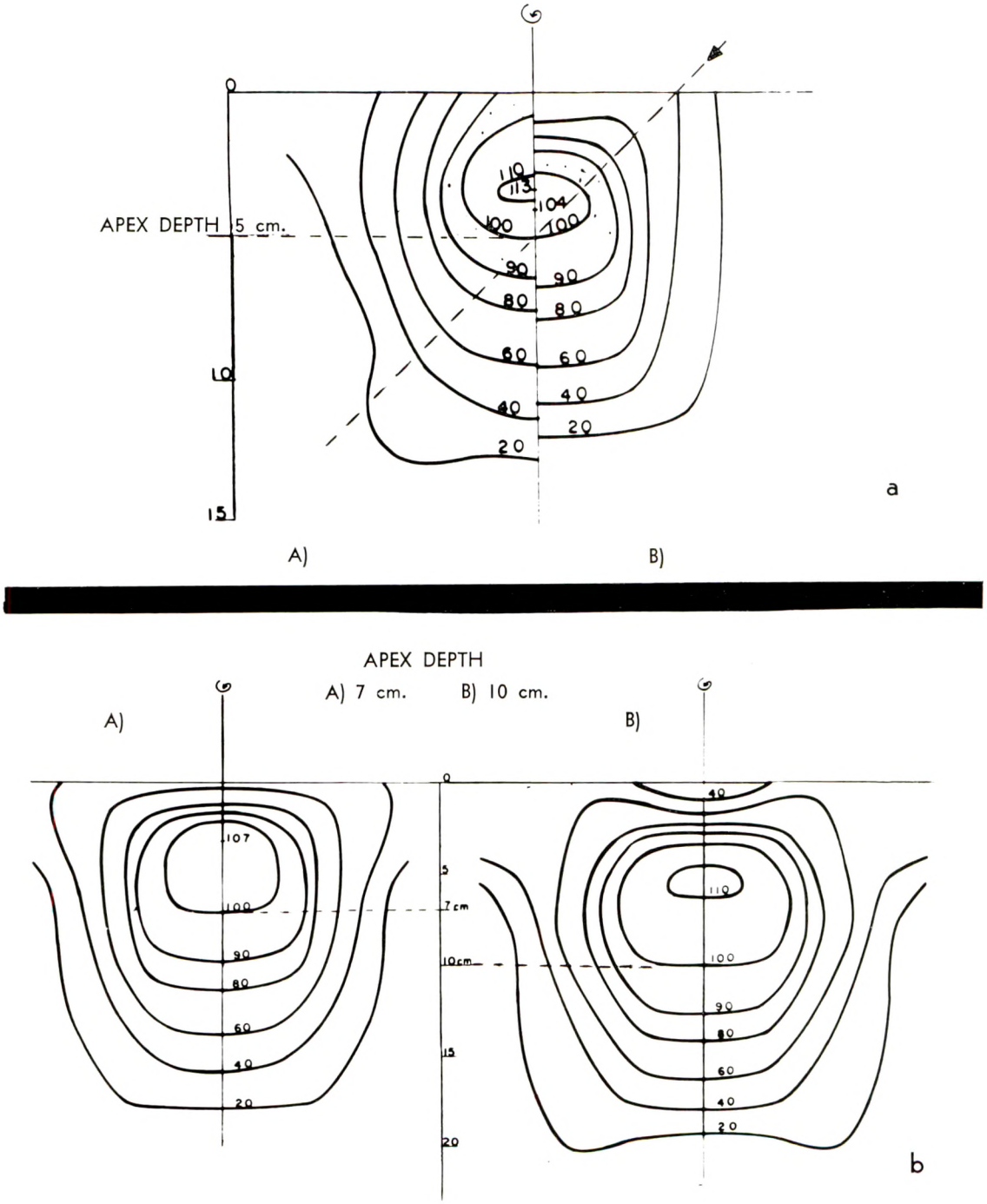


FIG. 5. Experimentally determined isodose charts for cobalt 60 short axis rotation (360°), angle of incidence 45°, 70 cm. source skin distance. (*a*) Comparison of depth dose distribution for 6×6 cm. field at 70 cm. source skin distance and 5 cm. apex depth, using A) regular collimation with an identical situation B) using extracollimation and 16.8° slope copper wedge filter. (*b*) Isodoses obtained by using a 10×10 cm. field at 70 cm. source skin distance, extracollimation and the 25.5° slope copper wedge filter for apex depths of A) 7 and B) 10 cm.

TABLE VI

COBALT 60—SHORT AXIS ROTATION—360°—ANGLE OF INCIDENCE 45°—70 cm. S.S.D. COPPER WEDGE FILTER —16.8° SLOPE AND ADDITIONAL COLLIMATOR —SQUARE FIELDS

FACTORS TO DETERMINE r/MINUTE AT THE CENTER OF ROTATION*

Area Field at Surface ($cm.^2$)	Apex Depth (cm.)					
	Surface	2	4	6	8	10
25	.760	.624	.467	.370	.307	.263
35	.819	.686	.565	.445	.358	.295
45	.825	.698	.575	.465	.374	.300
55	.830	.700	.580	.468	.380	.303
64	.835	.705	.583	.470	.382	.308

* The r/minute at the center of rotation is obtained by multiplying the corresponding factor above by the output at 0.5 cm. below surface of the corresponding straight field when extra-collimation is used. To obtain rad/minute multiply the r/minute by 0.97.

allowing for 2 mm. gap and 2 mm. plateau, is calculated as (L-0.4) cm., where L is the length of the aperture of the final collimator. The maximum thickness of the wedge is obtained by: plateau thickness $= \tan \theta$ (L-0.4) cm. where θ is the slope and L, as above, the length of the aperture of the additional collimator.

The results of the addition of the extra-collimation and the 16.8° slope copper wedge filter are presented: (1) in the isodose charts for 360° rotation shown in Figures 3*b*; and 4, *a* and *b*, where field sizes of 5.5×5.5; 6×6; 6.7×6.7 and apex depths from the surface to 10 cm. below the surface were used; (2) in Tables IV and V for depth doses along the axis of rotation for areas from 25 to 64 square centimeters at the surface and apex depths from surface to 10 cm. below the surface. Table VI was calculated to give the r/minute factors for the additional collimator and 16.8° slope copper wedge filter. The 100 per cent figure for short axis rotation, taken arbitrarily at the apex, is related to the 100 per cent of the identical straight field at 0.5 cm. below the surface, when the additional collimator is used without wedge.

Comparison of our depth dose tables for orthotherapy, obtained when the additional collimator for square fields is used, and Johns' depth dose tables[1] shows good agreement. This leads one to expect only small differences in the depth dose along the axis of rotation if short axis rotation is used with cobalt 60 units with any type of penumbra trimmer that reduces the penumbra to about 15 per cent at 1 cm. from the edge of the field at the surface. Greater differences may be expected for larger size penumbras.

The effect of the use of the additional collimation and the 16.8° slope copper wedge filter is presented in Figure 5*a*, where two isodose charts for complete rotation (360°) and for the same set of factors, with and without additional collimation and copper step wedge filter, are placed side by side. The reduction of the dose above and below the axis of rotation and the better homogeneity around the axis of rotation, with the additional collimation and the 16.8° slope copper wedge filter, are shown in Figure 5*b*. Two isodose charts for complete rotation, using a 10×10 cm. field at the surface (70 cm. source skin distance) and apex depths of 7 and 10 cm. are presented. The increase in the slope angle of the wedge when fields of more than 7×7 cm. are used improved the homogeneity around the apex appreciably as compared to the one obtained using only the 16.8° wedge.

SUMMARY

The physical aspects of short axis rotation therapy are discussed. Isodose improvements made by the addition of wedge filters and extracollimation to the standard cobalt 60 teletherapy unit are described. A number of isodose curves and depth dose tables are presented.

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SHORT AXIS ROTATION WITH COBALT 60 TELETHERAPY UNIT, USING COPPER WEDGE FILTERS AND SQUARE FIELDS*

PART II. CLINICAL ASPECTS

By VICTORIA CASTRO *and* WAYNE P. WHITCOMB, M.D.
NEW HAVEN, CONNECTICUT

ALTHOUGH we are not rotation minded at the Radiation Therapy Center, Hospital of St. Raphael, we have extensively investigated the physical aspects of short axis rotation using the cobalt 60 teletherapy unit (see Part I). Clinical material for short axis rotation therapy has been highly selected and, therefore, not of great number or of statistical significance. Primary disease treated has been of the antrum, pharynx, tonsil, skin, lung, bladder, and prostate; secondary disease has consisted mainly of lymph node and skin metastases where conventional therapy is precluded because of previous irradiation.

To prevent inadvertent high dosage or extensive bookkeeping of rotation positions, all treatments have been given in whole multiples of the 360° rotation period (61 seconds) of our rotation table. For simplicity and accuracy, the pin and arc set-up was used and checked through a complete rotation before beginning treatment. The assumption is made that the patient presents a horizontal planar skin surface to the perpendicular axis of rotation.

Four illustrative cases of the method are presented. Cases III and IV enable a clinical comparison between the non-wedge and the wedge filter technique.

ILLUSTRATIVE CASES

CASE I. (Fig. 1*a*). D.S., a 49 year old male, presented with thrice recurrent, extensive and diffuse papillary carcinoma of the bladder previously treated by fulguration. His general health was excellent. The isodose pattern of the treatment situation is presented. The dose delivered was approximately 4,300 r at the 90 per cent and 4,800 r at the 100 per cent isodose level in a period of 29 days. At the conclusion of therapy there was considerable dysuria which cleared up one month after treatment. The patient died 24 months later. The cause of death by autopsy findings was coronary sclerosis with acute myocardial insufficiency. No evidence of carcinoma of the bladder was found.

CASE II. (Fig. 1*b*). C.W., a 75 year old active male, suffered from frost bite of the left ear 50 years previously. Five years prior to admission to the Hospital of St. Raphael, the patient developed an epidermoid carcinoma of the ear which was treated with surgery and radiation therapy elsewhere. During the past 2 to 3 years he had noted a gradually enlarging, ulcerating mass below the remnants of the left ear. On examination this measured 6 cm. in greatest diameter and was elevated 1 cm. at its active edge. Pharyngeal examination disclosed bulging of the left lateral wall of the pharynx which was attributed to the pressure from the skin lesion. There were no enlarged lymph nodes. Due to the presumed deep extent and the shape of the tumor, cobalt 60 short axis rotation therapy seemed indicated. In a period of 32 days a tumor dose of 5,500 r was delivered by short axis rotation with an average apex depth setting of 3 cm. Within 3 months the lesion had completely healed. The patient did well for 15 months after treatment until he contracted pneumonia and expired of septicemia. At autopsy no evidence of tumor was found.

CASE III. (Fig. 1*c*). M.A., a 70 year old female, presented with a proven adenocarcinoma of the right maxillary antrum. The patient complained of swelling of the right face of 6 weeks' duration. At the initial examination the right cheek was

* From the Radiation Therapy Center of the Hospital of St. Raphael, New Haven, Connecticut. Supported by a grant in aid from the local division of the American Cancer Society.
Presented at the Forty-fourth Annual Meeting of the American Radium Society, New York City, April 2–4, 1962.

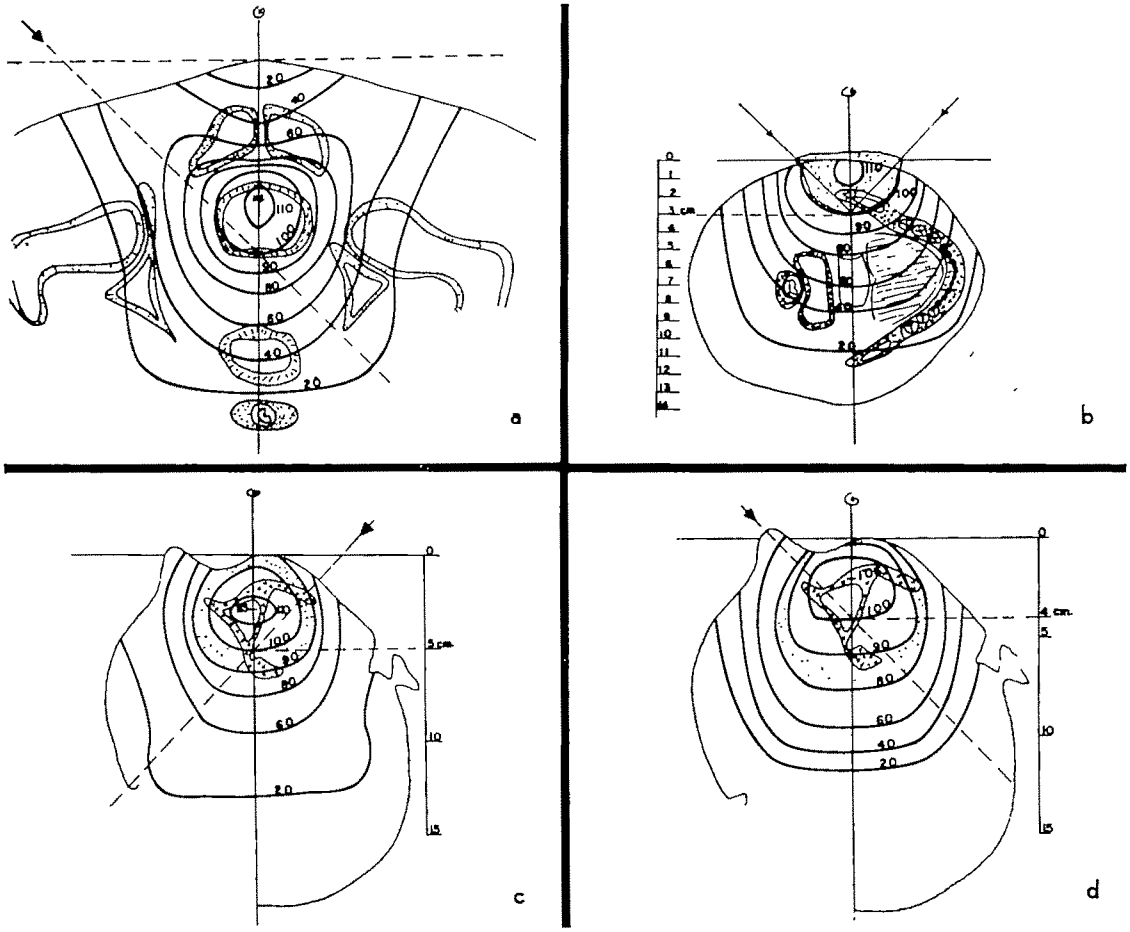


FIG. 1. Illustrative cases treated by cobalt 60 short axis 360° rotation at an incidence angle of 45° and a 70 cm. source skin distance. (*a*) Case I. *Papillary carcinoma of the bladder.* Regular collimator; 5×5 cm. field at surface; apex depth 10 cm.; tumor dose 4,780 r in 29 days. (*b*) Case II. *Epidermoid carcinoma of the skin invading the lymphatics.* Regular collimator; 6×6 cm. field at surface; combined isodose from 100 per cent=3,388 r with center of rotation 4 cm. below surface and 100 per cent=2,106 r with center of rotation 2 cm. below surface; effective dose from 100 per cent at center of rotation of 3 cm. depth=5,494 r in 32 days. (*c*) Case III. *Adenocarcinoma of the right maxillary sinus.* Regular collimator; 6×6 cm. field at surface; center of rotation 5 cm. below surface; dose 100 per cent=6,693 r and 90 per cent=6,024 r in 38 days. (*d*) Case IV. *Undifferentiated carcinoma of the right antrum.* Extra collimator and 16.8° slope Cu wedge filter; 6.7×6.7 cm. field at surface; center of rotation 4 cm. below surface; dose 100 per cent=7,222 r and 90 per cent=6,500 r in 36 days.

swollen, and there was injection of the right conjunctiva but no diplopia. There was edema of the right alveolar ridge. The antrum had been biopsied transnasally. Roentgenograms showed destruction of the roof, anterolateral margin, medial wall, and floor of the antrum. The patient was treated with cobalt 60 short axis rotation without wedge filter or additional collimation to an antral tumor dose of 6,700 r in 38 days at the 100 per cent isodose level. The left eye was shielded. The maximum skin reaction was a first degree epithelitis; the palatine mucosa and adjacent tongue showed second to third degree mucositis. The patient has had several antral biopsies since treatment, showing no evidence of tumor in the sinus. Two years later she presented with a high dose reaction at the right lateral aspect of the middle third of the tongue and also early cataract formation in the right eye.

CASE IV. (Fig. 1*d*). C.C., a 57 year old female,

presented with a 5 month history of a watering eye followed by the appearance of a mass in the right paranasal area. Needle biopsy showed undifferentiated malignant cells. At the initial physical examination the tumor was noted to be invading the floor of the orbit, nasal cavity, and cheek but did not appear to have penetrated the floor of the sinus or the canine fossa. The patient was treated by cobalt 60 short axis rotation with wedge filter and additional collimation to a tumor dose ranging from 6,450 r at the 90 per cent to 7,200 r at the 100 per cent isodose level in a period of 36 days. At the conclusion of therapy there was brisk second degree mucositis at the junction of the soft and hard palates and some mucositis of the tongue as well as epithelitis of the skin overlying the antrum and nose. The patient is alive and well 8 months after therapy. The pupil of the unprotected right eye became dilated and fixed due to synechiae but is now responding to therapy by an ophthalmologist.

DISCUSSION

Cobalt 60 short axis rotation has been used in diverse palliative and curative treatment situations alone and in combination with conventional cobalt 60 teletherapy. We believe that selection of patients is important in order for the disease and the isodose patterns to be congruent. We feel that cobalt 60 short axis rotation is an important approach to curative disease of at least the bladder and antrum. It is a very useful palliative method in certain nasopharyngeal lesions and lung malignancies and in certain highly selected superficial lesions where other modalities of treatment are precluded or difficult to use.

SUMMARY

Four clinical instances of the use of cobalt 60 short axis rotation therapy are presented. The sites of disease include the bladder, skin, and antrum.

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AN OPTICAL TREATMENT DEPTH GAUGE FOR TELETHERAPY UNITS*

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ONE of the essential measurements in multifield and rotation therapy is the distance from the skin to the center of the treated volume. In fixed field therapy it is necessary to know this distance along each field axis for accurate dosimetry. In rotation therapy distances from the skin to the axis of rotation must be known both for setting up the patient and for calculating the tumor dose.

In this article a simple gauge is described which permits rapid and accurate measurement of treatment depths and, because it relies on optical projection of a scale onto the patient's skin, does not cause any mechanical obstruction of the space between radiation source and patient.

The principle of such a gauge is illustrated in Figure 1. A simple light projector consisting of a pair of condenser lenses and a projection lens is mounted at the side of the treatment head. A reticle calibrated in such a way that it represents centimeter divisions when imaged along the radiation beam axis is projected onto the patient. The distance from the skin to the tumor position is indicated by the intersection of the projected scale division and the central spot of the field-defining light-beam projected along the treatment axis.

The gauge is particularly useful with isocentric treatment units. Setting-up is performed from a knowledge of the depth of the treatment volume beneath any chosen skin mark, not necessarily vertically above the center of the volume. The depth of overlying tissue in any direction chosen for a particular treatment field can then be read with ease from the optical depth gauge merely by swinging the unit to the appropriate angle. For arc rotation, treatment depths can quickly be measured at intervals of, say, 15 degrees of arc with the gauge. In full 360 degree rotation it is our practice to make transit dose measure-

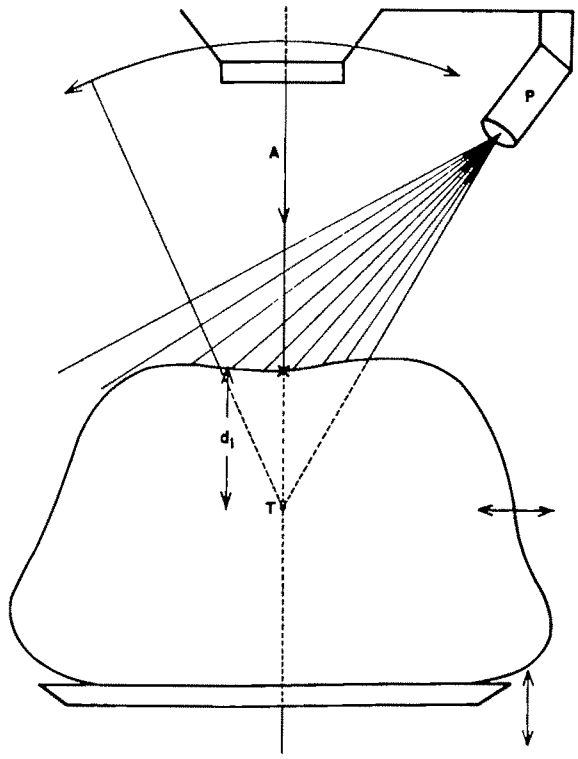


FIG. 1. Schematic representation of optical depth gauge. P is the projection system consisting of a light source, pair of condenser lenses, reticle and projection lens. T is the center of rotation, at a distance of 55 cm. from the source of the Theratron Jr., 27 cm. from the front face of the beam head and about 50 cm. from the front of the projector P. The reticle projects parallel lines spaced at centimeter intervals along AT, spanning a total distance of 22 cm. from the "zero" line at T. The tissue depth d_1 is read on the skin surface at the intersection of the projected scale division with the central cross shadowed by the field-defining light-beam along the beam axis A. Distances from axis T to skin surface may be read with the beam head at any desired angle.

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ments to obtain a knowledge of the radial distances, and hence the optical gauge is not used in these cases except for initially setting-up the patient with the tumor at the axis of rotation.

It is found that distances can easily be read to the nearest millimeter, and both setting-up and dosimetry are greatly facilitated.

The distance gauge (Fig. 2) in use in this Clinic was designed by us for the Theratron Jr. telecobalt unit, which has a source-to-axis distance of 55 cm. Calculations were made to determine the focal lengths and diameters of the optical parts so as to focus the scale at a distance of about 50 cm. from the projector and to span a range of treatment depths from 0 to 22 cm. The reticle was calibrated by use of a trial reticle carrying uniform divisions which were projected onto centimeter paper placed along the treatment beam axis, and hence a calibration curve could be obtained for the required spacing of the lines. For treatment units with source-to-axis distances of more than 55 cm., some of the design requirements such as size of angular field and focal length may prove simpler to fulfill, and the problem of mounting the projector out of the way also will be less difficult.

This instrument has proved to be reliable, accurate, simple to use and maintain, and inexpensive. Lenses need not be of high quality since aberrations are of no great importance as only a series of short parallel lines are projected, and the reticle is calibrated to suit the required conditions. The mounting must be quite rigid, and lenses, reticle and light source must be firmly attached.

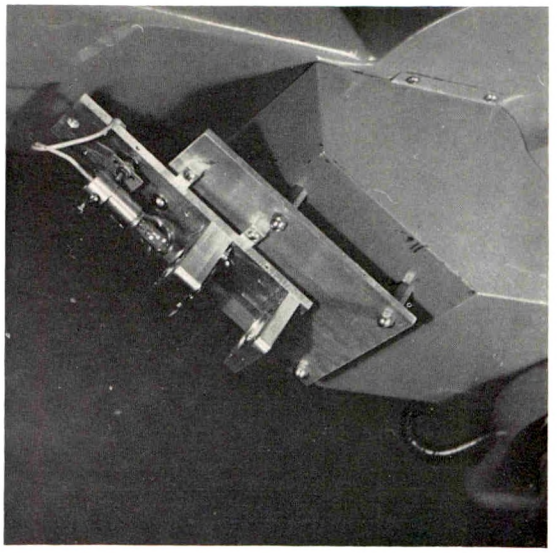


Fig. 2. Optical projector (cover removed), mounted on head of Theratron Jr. hectocurie cobalt 60 unit, showing projection lens, reticle, condenser lenses and light bulb.

SUMMARY

A simple optical projector is described which, by casting the image of a centimeter scale, parallel to the treatment beam axis, onto the patient, permits rapid reading of treatment depth in setting-up and in dosimetry with teletherapy equipment.

The Ontario Cancer Foundation
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The execution of the mechanical design of the projector is due to Mr. A. Edney, instrument maker of this Clinic. A projection gauge of this kind is at present available for use with the AECL Theratron cobalt unit (source-to-axis distance 75 cm.) as an optional accessory.

FAT ABSORPTION FROM THE HUMAN GASTRO-INTESTINAL TRACT IN PATIENTS UNDERGOING TELETHERAPY*

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THE effects of ionizing radiation on the gastrointestinal system have been studied from many aspects. At this institution we have been interested, primarily, in the effect on fat absorption. The development of an accurate and simple method of evaluating to some degree the function of the intestines with regards to fat absorption by Baylin *et al.*[1] and Sanders *et al.*[5] has greatly facilitated this study. Modification of the technique to utilize capsules of the neutral fat or a fatty acid (oleic acid) has enhanced our ability to carry out investigations such as this.[2,3]

In 1959 a systematic evaluation of all patients undergoing conventional roentgen therapy (200 kv. peak) to the lower abdomen was carried out using glyceroltrioleate and oleic acid absorption studies.[4] It was found that there was a deficiency in absorption in 45 per cent of the patients at some time during the course of their therapy. The highest incidence was in the third week with a midline tissue dose of about 2,000 r to the lower abdomen. The fecal radioactive recovery test was found to be more sensitive than the blood level determinations in this study.

It is the purpose of the present article to give the results of an investigation on a similar group of patients undergoing cobalt 60 teletherapy irradiation to the lower abdomen and to compare these findings with those of the previous one.

METHODS AND MATERIALS

This investigation has been carried out in a manner identical to that of the 1959 series except that cobalt 60 teletherapy was employed instead of 200 kv. peak roentgen therapy. Twenty-five consecutive patients undergoing cobalt 60 therapy to the lower abdomen were studied. They were alternately assigned to be studied throughout the course of therapy with either glyceroltrioleate or oleic acid absorption tests. Each patient had two tests carried out per week unless his condition or other circumstances dictated otherwise; one of them was studied with blood and fecal analysis and one with fecal analysis only.

The investigation utilized capsule test meals of either glyceroltrioleate or oleic acid. Blood samples were drawn at 4, 5 and 6 hours after administration of the test meal. Radioactive analysis was carried out in routine manner and the radioactivity in the total blood volume was determined. Fecal collections were made and analysis was carried out to determine the total amount of radioactive material excreted in the feces over a period of 48 hours. Fecal excretion of more than 3 per cent of the ingested radioactivity was considered abnormal.

RESULTS

A total of 125 blood studies was performed, each consisting of 3 individual analyses of samples drawn at 4, 5 and 6 hours sfter administration of the test meal. A total of 201 fecal analyses was performed to determine the radioiodine content in the 48 hour stool.

Figure 1 shows the percentage of patients with abnormal fecal recoveries as a function of radiation dosage at the midline

* From the Department of Radiology, Duke University Medical Center, Durham, North Carolina. Supported in part by Grant No. C 2602 (C4) USPH.

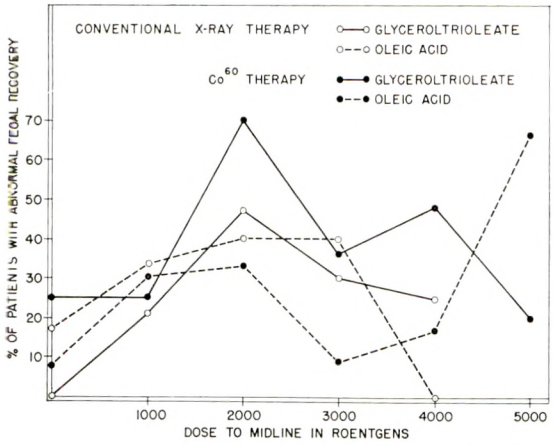


FIG. 1. Percentage of patients showing abnormal absorption studies with a comparison to midline doses.

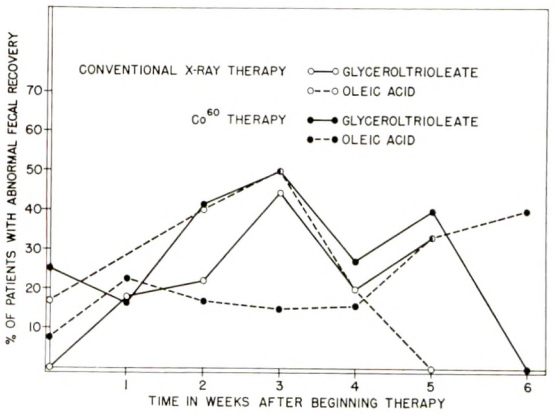


FIG. 2. Percentage of patients showing abnormal absorption studies with a comparison to time in weeks after beginning of therapy.

of the therapy field. The curves for both glyceroltrioleate and oleic acid studies are given.

Figure 2 shows the percentage of patients with abnormal fecal recoveries as a function of time after initiation of the course of both cobalt 60 teletherapy and conventional roentgen therapy. The results for both the oleic acid and glyceroltrioleate absorption studies are included.

Figure 3 is a comparison of the time and the dose with the abnormal fecal recovery tests. This includes glyceroltrioleate studies only for both cobalt 60 teletherapy and conventional roentgen therapy.

Table 1 gives the actual number of patients having abnormal fecal recovery at 1,000 r increments of dose to the midline of the therapy field. Table II gives the number of patients having abnormal fecal recovery

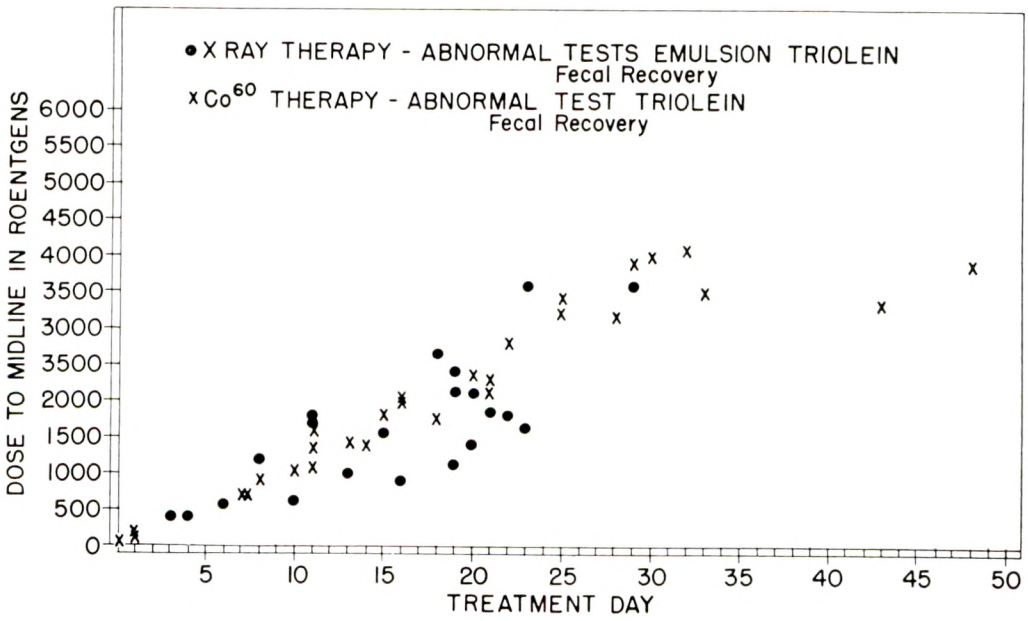


FIG. 3. Patients showing abnormal fecal recoveries with triolein with a comparison to treatment day and midline dose.

TABLE I

NUMBER OF PATIENTS SHOWING ABNORMAL FECAL RADIOACTIVITY RECOVERIES AND DOSAGE TO MIDLINE

Dose to Midline of Body (r)	Conventional 200 kv.p. Therapy		Cobalt 60 Teletherapy	
	Glycerol-trioleate	Oleic Acid	Glycerol-trioleate	Oleic Acid
0	0 of 17	1 of 6	3 of 12	1 of 13
1,000	4 of 13	2 of 6	3 of 12	3 of 12
2,000	8 of 17	2 of 5	7 of 10	4 of 12
3,000	3 of 10	2 of 5	4 of 11	1 of 11
4,000	1 of 4	0 of 1	5 of 11	2 of 11
5,000	—	—	1 of 5	4 of 6

TABLE II

NUMBER OF PATIENTS SHOWING ABNORMAL FECAL RADIOACTIVITY RECOVERIES AND TIME IN WEEKS AFTER START OF THERAPY

Time after Start of Therapy (wk.)	Conventional (200 kv.p.) Therapy		Cobalt 60 Teletherapy	
	Glycerol-trioleate	Oleic Acid	Glycerol-trioleate	Oleic Acid
0	0 of 17	1 of 6	3 of 12	1 of 13
1	3 of 16	—	2 of 12	3 of 13
2	4 of 18	2 of 5	5 of 12	2 of 11
3	8 of 18	3 of 6	6 of 12	2 of 13
4	2 of 10	1 of 5	3 of 11	2 of 12
5	1 of 3	0 of 2	4 of 10	3 of 9
6	—	—	0 of 6	2 of 5

at weekly increments of time after beginning therapy.

Table III shows the number of tests in which the blood and fecal analyses agree and disagree, in both the conventional roentgen therapy series and the cobalt 60 series, with the use of both glyceroltrioleate and oleic acid. It may be noted that there is a greater number of disagreements in the cobalt series than in the conven-

TABLE III

TEST AGREEMENT TABLE IN CASES HAVING SIMULTANEOUS BLOOD AND FECAL ANALYSIS

Blood	Fecal	Conventional Roentgen Therapy		Cobalt 60 Teletherapy	
		Agree	Disagree	Agree	Disagree
		Glyceroltrioleate Studies			
Normal	Normal	63		23	
Normal	Abnormal		13		6
Abnormal	Normal		0		13
Abnormal	Abnormal	1		13	
Total		64	13	36	19
		Oleic Acid Studies			
Normal	Normal	15		32	
Normal	Abnormal		5		4
Abnormal	Normal		1		9
Abnormal	Abnormal	1		2	
Total		16	6	34	13

Table IV

TOTAL OF TESTS PERFORMED WITH PERCENTAGE OF ABNORMAL FINDINGS

	Glyceroltrioleate Studies			Oleic Acid Studies		
	Total Tests	Abnormal Tests	Per Cent of Abnormal Tests	Total Tests	Abnormal Tests	Per Cent of Abnormal Tests
Conventional Roentgen Therapy						
Blood Analyses	77	1	1.3	22	2	9.1
Fecal Analyses	121	17	14.10	31	9	29.0
Cobalt 60 Teletherapy						
Blood Analyses	59	27	45.7	33	15	45.5
Fecal Analyses	94	29	32.4	105	16	14.7

tional roentgen therapy series.

Table IV summarizes the number and percentage of tests which were normal and abnormal in both types of therapy. The marked increase in the percentage of abnormal fecal tests as compared to the blood tests may be noted in the conventional roentgen therapy series. There is a less striking difference in the cobalt 60 series although a definite reversal of these findings is noted. There is an increased percentage of abnormal tests in the cobalt treated group as compared to that of the conventional roentgen therapy series.

DISCUSSION

A comparison of the curves obtained in conventional roentgen therapy and cobalt 60 teletherapy series shows a "peaking" of both curves with glyceroltrioleate at about 2,000 r calculated dosage to the midline of the therapy field. This would indicate that the absorption and/or digestion is affected most when the tissue dose to the midplane of the body has reached approximately 2,000 r. One may also note that there is a slightly increased incidence of malabsorption or maldigestion of glyceroltrioleate in those patients treated with cobalt 60 teletherapy. In evaluating the significance of this difference, however, one must recognize that the groups are not large and that the incidence of abnormality in the preirradiation control study is lower in the conventional roentgen therapy series (0 of 17) than in the cobalt 60 series (3 to 12). It is quite possible that these factors might be responsible for the apparent increase in malabsorption or maldigestion in the patients undergoing cobalt 60 therapy as compared to those having conventional roentgen therapy.

The reverse situation is present in the study of oleic acid absorption. There is relatively little difference between the overall level of the curves in both types of therapy; however, the small number of patients in the conventional roentgen therapy series must be taken into consideration.

A comparison of the percentage of patients with abnormal fecal recovery as a function of time from the beginning of therapy shows the "peaking" effect at about 3 weeks in both the conventional roentgen therapy and the cobalt 60 teletherapy series. The one exception to this is the oleic acid absorption studies done in those patients receiving cobalt 60 therapy. There is no "peaking" seen in this curve.

There was a slight difference in the oleic acid abnormality curve level when compared to the glyceroltrioleate abnormality curve level throughout the entire study. Toward the end of the course of therapy a very definite trend toward a decrease in the incidence of malabsorption in the group as a whole and in the individual patients was noted. This may represent a tolerance or recovery phase.

Tables I and II show the changes seen on the curves but also point out that percentage may be deceiving. The highest incidence of abnormality is again noted to be at 2,000 r midline dose and 3 weeks of therapy.

Table III gives the number of tests performed simultaneously in which the results of the blood analyses and fecal analyses agree and disagree. There is a definite increase in the number of disagreements in the cobalt 60 series studied with glyceroltrioleate as compared to the conventional roentgen therapy series. It may be noted also that there is an increase in the number of abnormal blood tests with normal fecal values. Some of this may be due to incomplete collection of feces or to poor emptying of the stomach. A review of the roentgenograms made during the sixth hour of the tests of the patients with low blood levels showed that on 4 occasions there was gastric retention of portions of the test meal. At least one patient was known to have eaten on several occasions during the period of the test. In this case the blood levels were depressed, but the fecal recovery was not affected.

Table IV shows the very striking over-all increase in abnormality in the cobalt 60 series as compared to that of the conventional roentgen therapy series. This is true of both the glyceroltrioleate and oleic acid studies. It also shows the greater percentage of blood abnormalities as compared to the fecal abnormalities in the cobalt 60 teletherapy group. This is the reverse of the findings in the conventional roentgen therapy group.

CONCLUSIONS

1. Patients undergoing radiation therapy to the lower abdomen develop evidence of malabsorption of glyceroltrioleate and oleic acid.

2. There is no definite evidence of interference with digestion of glyceroltrioleate.

3. In this series of cases, the highest incidence of malabsorption took place at about 3 weeks in the course of therapy with a radiation dosage to the midline of the body of about 2,000 r.

4. A recovery phase appears to occur after this midline dosage is achieved and after the third week of radiation therapy.

5. There is a greater percentage of abnormal total tests and of patients with abnormal tests in the cobalt 60 therapy group than in the conventional roentgen therapy group.

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LEIOMYOSARCOMA OF THE ESOPHAGUS*

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LEIOMYOSARCOMA is an extemely rare neoplasm of the esophagus, only 20 cases having been reported in the literature. The first documented smooth muscle sarcoma of the esophagus was reported by Howard[4] in 1902. Isolated reports have appeared since then and a few such cases have been treated successfully by surgery. Little if any mention is made in the literature concerning the use of radiation therapy in the management of these tumors. For this reason an additional case, in which the sarcoma showed a dramatic response to supervoltage therapy, is being reported from the University of Maryland Hospital.

REPORT OF A CASE

This sixty-two year old white male was referred to the Department of Radiation Therapy in March, 1958 for definitive treatment of a large tumor of the proximal third of the esophagus. The patient had first noticed difficulty in swallowing and pain referable to the hypopharynx four months prior to his initial visit. During the following three months he had lost 18 pounds in weight and had noted hoarseness. He had been hospitalized in another local institution, where roentgenographic studies revealed a large expansile tumor of the proximal esophagus (Fig. 1, *A* and *B*). Biopsy of the lesion was interpreted as squamous cell carcinoma and the patient was referred for radiation therapy.

Physical examination revealed a well-developed, well-nourished white male who did not appear chronically ill. Paralysis of the left vocal cord was the only positive physical finding. The unusual size of the tumor and the excellent condition of the patient were thought to be somewhat incongruous for an esophageal tumor of mucosal origin; a review of the biopsy material was obtained and a final diagnosis of leiomyosarcoma was established (Fig. 2, *A* and *B*). The size of the mass and the evidence of involvement of the left recurrent laryngeal nerve were felt to be contraindications for attempted surgical extirpation of the tumor.

A course of supervoltage irradiation (Co^{60}) was instituted; a tumor dose of 5,700 r was delivered in five and one-half weeks utilizing parallel opposing fields and a rotational technique. The patient responded well to treatment, being able to take both liquids and solids without difficulty at the completion of therapy. At the same time, normal motion of the left cord was observed. Repeat esophagrams three weeks after therapy revealed marked regression in the size of the tumor (Fig. 3, *A*, *B* and *C*).

Because of the presence of obvious residual tumor demonstrated roentgenographically in the proximal esophagus, it was felt that surgical removal of the residual disease offered the patient the only hope of complete cure. In July, 1958, eight weeks after the completion of radiation therapy, esophageal resection and mobilization of the right colon and terminal ileum into the mediastinum was performed. Only a small 1 cm. nodule of residual tumor could be found in the proximal esophagus. The patient did well until the sixth postoperative day, at which time clinical evidence of disruption of the proximal ileo-esophageal anastomosis developed. Despite therapy, the patient died in acute respiratory distress on the ninth postoperative day.

Autopsy revealed necrosis of the ileo-esophageal anastomosis with secondary empyema, mediastinitis, pericarditis and peritonitis. No evidence of residual or metastatic tumor was found.

DISCUSSION

As best as can be determined from the available case reports, esophageal leiomyosarcomas occur as either polypoid or infiltrating tumors; a few have been described as polypoid intraluminal masses on a pedicle. They commonly involve the middle and lower thirds of the esophagus. All of the patients have had dysphagia in varying degrees, although the symptoms have been of less severity and of longer duration in

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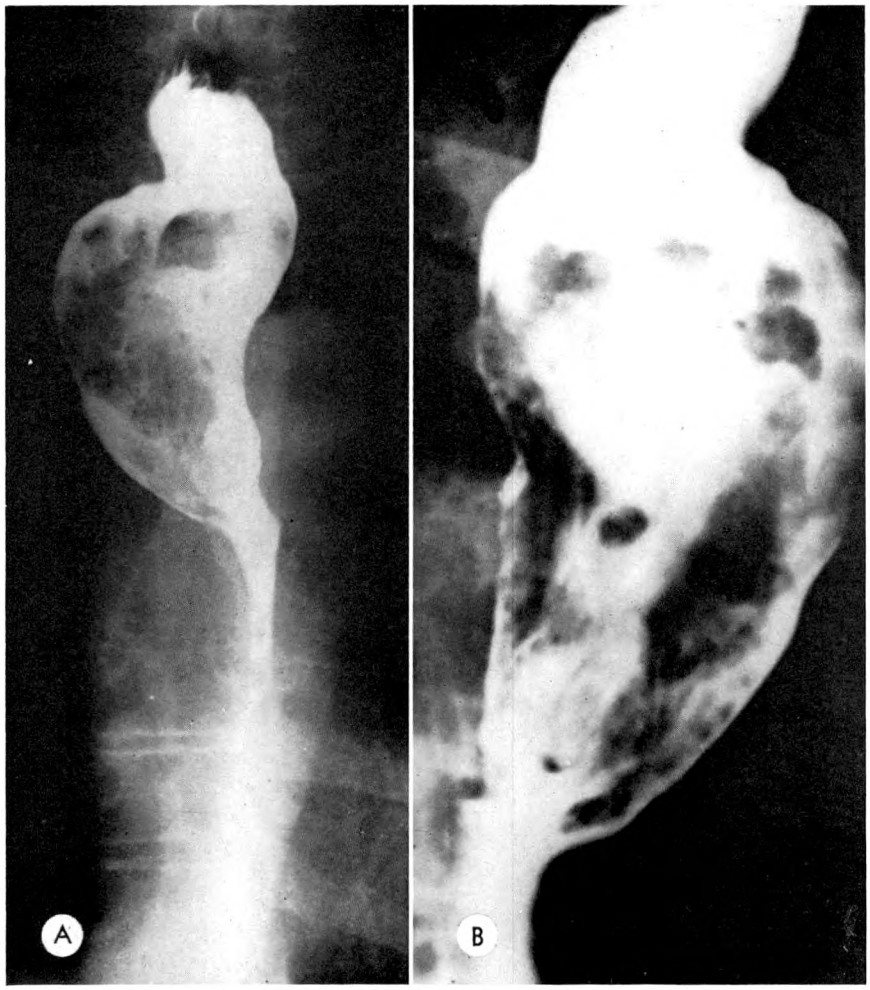


Fig. 1. (*A* and *B*) Pretreatment esophagrams (March, 1958) revealing a large polypoid leiomyosarcoma of the proximal esophagus.

comparison to those related to esophageal malignancies of mucosal origin. The diagnosis is usually established by esophagoscopy and biopsy, although, as in this case, the erroneous histologic diagnosis of squamous cell carcinoma may be made.

Roentgenographically, the tumor does not always present as a typical intramural esophageal mass, the infiltrating type being indistinguishable from an esophageal carcinoma. However, the presence of a large expansile polypoid tumor which does not appreciably obstruct the esophageal lumen should suggest the possibility of a leiomyosarcoma, since such findings are unusual for an esophageal carcinoma. A very large leiomyosarcoma may even present as a mediastinal mass. In contradistinction to tumors of mucosal origin, esophageal leiomyosarcomas are usually indolent low-grade sarcomas with infrequent metastases; therefore, therapeutically, one is concerned basically with the control of the primary lesion.

Successful surgical extirpation of an esophageal leiomyosarcoma has been reported by several authors[1,3,5,7,8] and it has seemed that surgery is the only logical definitive therapeutic approach. However, radiation therapy may be of some value in dealing with advanced bulky tumors and may, in fact, make them amenable to surgi-

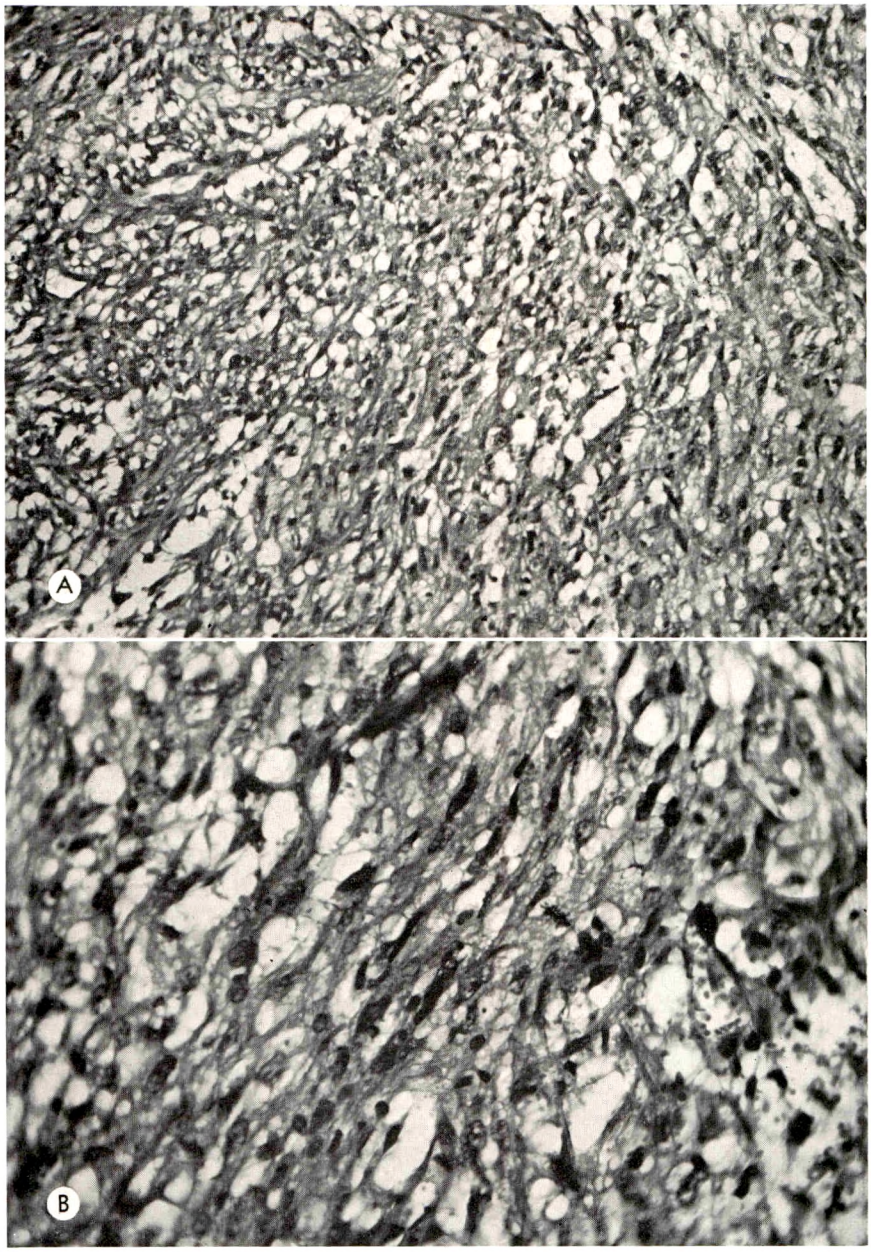


Fig. 2. (*A* and *B*) Photomicrographs of sections of the tumor prior to radiation therapy. There is moderate pleomorphism of the spindle cell stroma. The nuclei are displaced to one side by the frequently vacuolated cytoplasm. Mitotic figures are present.

cal excision. Little if any information is available in the literature concerning the use of ionizing radiation in dealing with these tumors. Menne and Birge[9] in 1935 employed local radium and external roentgen therapy in treating a very advanced leiomyosarcoma of the proximal esophagus. The patient experienced transient relief of dysphagia but died shortly after the completion of therapy. Pennes[11] in 1942 treated a leiomyosarcoma of the midesophagus with 200 kv. roentgen rays and commented that the patient was slightly improved after the completion of therapy. Watson, in

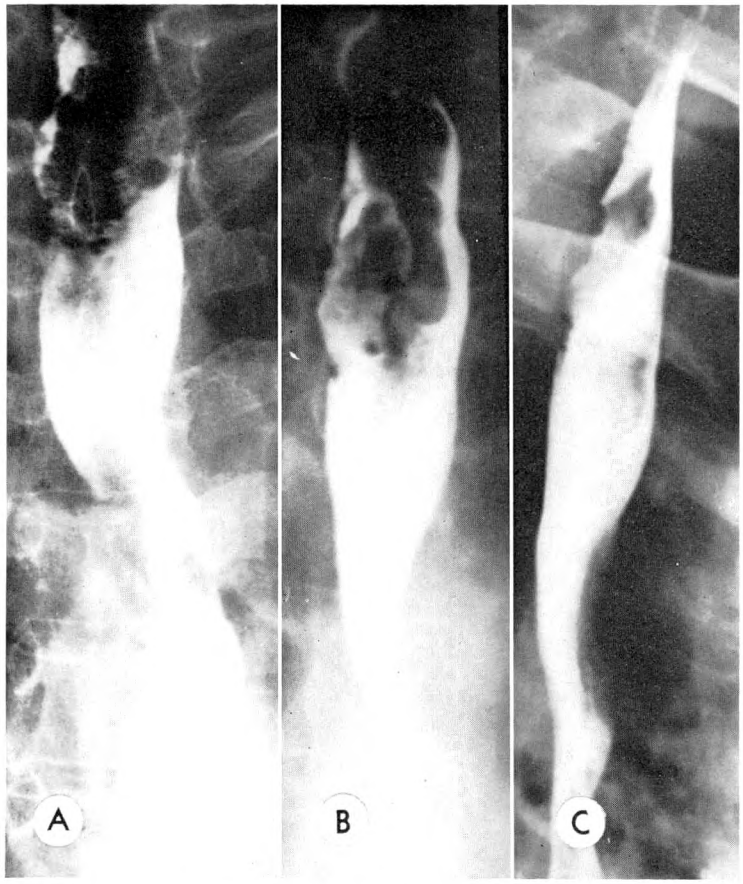


Fig. 3. (*A*, *B* and *C*) Esophagrams three weeks after the completion of radiation therapy (June, 1958) showing marked regression in the size of the tumor; residual sarcoma is still apparent.

1954, in the discussion of a paper of Sweet *et al.*,[12] mentioned 4 patients with esophageal leiomyosarcomas. One of these, who was biopsied only at the time of thoracotomy, had a gastrostomy performed and was treated with roentgen rays. The patient is alive and well five years later.

Although leiomyosarcomas have been considered radioresistant tumors, the remarkable response to irradiation seen in the case being reported would suggest that this premise may not necessarily be true. With the advent of higher energy radiation devices and the concomitant ability to deliver greater doses, the concept of radioresistance of sarcomas has been subject to re-evaluation. It should be emphasized that an adequate tumor dose can be delivered only by utilization of supervoltage rather than orthovoltage radiation. Until more information can be gathered, it would appear that large bulky esophageal leiomyosarcomas may be treated best by a combination of preoperative supervoltage irradiation followed by surgical excision. Very advanced tumors, for which only palliation is deemed feasible, could be managed by irradiation alone, while less advanced smaller lesions would lend themselves to surgical therapy.

SUMMARY

1. An additional case of a leiomyosarcoma of the esophagus is added to the limited number already reported.

2. Remarkable regression of the tumor occurred with supervoltage radiation therapy which reduced the tumor to such a size that surgical extirpation was feasible.

3. Radiation therapy should not categorically be deemed useless in dealing with these tumors; this therapeutic modality would appear to be of benefit in the preoperative management of large esophageal leiomyosarcomas as well as in palliation.

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SARCOMA OF THE ESOPHAGUS*

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SARCOMA of the esophagus is a rare disease. Reports in the literature consist of isolated 1 or 2 cases by different authors. Camishon *et al.*[2] in 1961 reviewed the literature on leiomyosarcoma of the esophagus and reported on 21 cases from the literature beginning with the first described case by Howard[5] in 1902 through their own 2 cases recorded in 1960. There were 14 males and 7 females in this collected series. The ages of the men varied from 38 to 70, and those of the women from 56 to 75. Nine of the cases were treated by resectional surgery (partial esophagectomy and esophagogastrostomy), 1 by local excision, and 2 by radiation therapy and gastrostomy. One each had laparotomy, thoracotomy or gastrostomy only. One had drainage of a mediastinal abscess secondary to perforation. The remaining 5 had no treatment. Of the 9 cases treated by resection and anastomosis of the esophagus, 1 died on the sixth postoperative day, 3 survived from 2 to 8 months with an average of 4.3 months, in 1 the survival was not stated, and in the remaining 4 the survival time was from 2 to 7 years with an average of 5.5 years. In the 2 cases treated by radiation, the average survival time was 2.5 months. The case treated by local excision survived 22 months.

In 1935, Jackson[6] found only 7 sarcomas in 935 cases of malignant esophageal neoplasms or an incidence of about 0.7 per cent. Thorek and Neiman,[9] reporting in 1950, listed 59 cases of sarcoma of the esophagus from the literature. The first case reported in 1877 by Chapman proved to be a fibrosarcoma. This list, however, included such diseases as melanosarcoma and lymphosarcoma, as well as fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma and unclassified sarcoma. These authors state that fibrosarcoma is the commonest sarcoma of the esophagus, and only 8 out of 59 were leiomyosarcomas. There were 27 fibrosarcomas. Camishon *et al.*[2] and Ovens and Russell[8] reported a case each in which there was associated squamous cell carcinoma and leiomyosarcoma of the esophagus.

Camishon *et al.*[2] believe that leiomyosarcoma is a very rare type of esophageal lesion despite the fact that the leiomyoma is probably the most common benign tumor encountered in this location. In their collected series, 7 were located in the upper third of the esophagus, 6 in the middle third, and 8 in the lower third. The tumors were either infiltrative or pedunculated. They state that the pathologic characteristic is of no significance as resection of either type has resulted in long term survival; however, a review of their report shows that the cases with an infiltrative type of lesion have not survived and that the long term survivors have had lesions of the polypoid type. In addition, an interesting fact is that all the long term survivors have been women.

The first successful resection of a leiomyosarcoma of the esophagus was performed by Harrington[4] in 1945 and reported in 1949. Lyons and Garlock[7] reported their case in 1951.

In 1959, Borrie[1] reported on the surgical treatment of sarcoma of the esophagus of 19 cases collected from the literature which were treated by resection. Five of these were women and 14 were men. The ages of the women ranged from 49 to 78 and those of the men from 43 to 75. In this group, there were 7 cases each of leiomyosarcoma and fibrosarcoma, 3 of rhabdomyosarcoma, 1 of fibroleiomyosarcoma and 1 diagnosed as sarcoma polymorphocellulare. In this selected group, there was no prepon-

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TABLE I

SUMMARY OF 8 CASES OF SARCOMA OF THE ESOPHAGUS

Case	Year	Patient	Age	Sex	Pathology	Duration of Symptoms	Location	Treatment	Survival Time
I	1946	A.L.	46	F	Myosarcoma	12 mo.	Distal	Resection of tumor	Still alive
II	1946	B.L.	58	F	Leiomyosarcoma	4 mo.	Distal	Resection of tumor	3 mo.
III	1948	A.G.	58	M	Leiomyosarcoma	5 mo.	Distal	Resection of tumor; esophagogastrostomy	55 mo.
IV	1948	E.G.	54	F	Fibrosarcoma	12 mo.	Cervical	Cervical esophagectomy	Still alive
V	1949	E.M.	58	F	Leiomyosarcoma	12 mo.	Upper	Exploration; irradiation	12 yr.
VI	1955	J.P.	50	M	Myosarcoma	5 mo.	Middle	Irradiation	2 mo.
VII	1956	H.H.	56	F	Leiomyosarcoma	6 mo.	Middle	Irradiation	17 mo.
VIII	1958	N.C.	74	F	Leiomyosarcoma	15 mo.	Distal	Resection of tumor; esophagogastrostomy	Still alive

derance of fibrosarcoma. As to location, 12 were in the lower third of the esophagus, 5 in the middle third, 1 in the upper third and 1 was classified as being in the upper and middle thirds. All cases except 3 were treated by resection and anastomosis (partial esophagectomy and esophagogastrostomy). The remaining 3 cases were treated by (a) enucleation, (b) subtotal esophagectomy without anastomosis, and (c) skin flap esophagoplasty (lesion in the upper third, presumably in the cervical esophagus). There were 4 postoperative deaths with an average survival of 10 days. Two cases survived 6 and 9 months, respectively, 1 having a recurrence in 6 months and expiring 3 months later. One case survived $2\frac{1}{2}$ years and then had a recurrence. In 4 cases, there was a survival of 2 to 7 years with an average of 5.5 years. One other was followed for a year without evidence of disease. In the remaining 8 cases, the follow-up was insufficient. In one of these latter cases, surgery was followed by deep roentgen therapy.

MATERIAL

Because of the rarity of this disease and because it was apparent that the prognosis in these cases, if adequately treated, is better than that of patients with carcinoma of the esophagus, we decided to report the cases of sarcoma of the esophagus treated at Memorial Hospital. There are 8 patients in this group and they represent the combined cases of several members of our staff, as well as those from the ward service of the Thoracic Surgical Service.

From 1926 through 1961, there have been 1,676 cases of cancer of the esophagus seen at our hospital. Of these, 173 have not been proven by biopsy or esophageal washings, and 47 have been excluded as possibly having their origin in the stomach. Thus there were 1,456 determinate cases of cancer of the esophagus of which there were 8 cases of sarcoma or an incidence of 0.5 per cent (Table 1).

In our group, there was a preponderance of females (6 females and 2 males) and the over-all average age was 56.7 years. The average age in the men was 54, whereas the average for the women was 57.7 (ranging from 46 to 74). All but 1 of the cases were classified as leiomyosarcoma (2 of these were called myosarcoma only). The exception was a fibrosarcoma, occurring in the cervical esophagus, and considered to be a radiation-induced tumor. This case was previously reported by Watson and Converse[10] and mentioned by Goodner and Watson.[3] Of the leiomyosarcomas, 4 were located in the distal thoracic esophagus, 2 in the middle, and 1 in the upper thoracic esophagus. Symptoms varied from 4 to 12 months with an average of 9 months. Five of the cases were treated by resectional surgery and 3 by radiation therapy. Of the 3 radiation treated cases, 2 survived 2 and 17 months, respectively, and the third survived 12 years. Two of the surgically treated cases are dead, having sur-

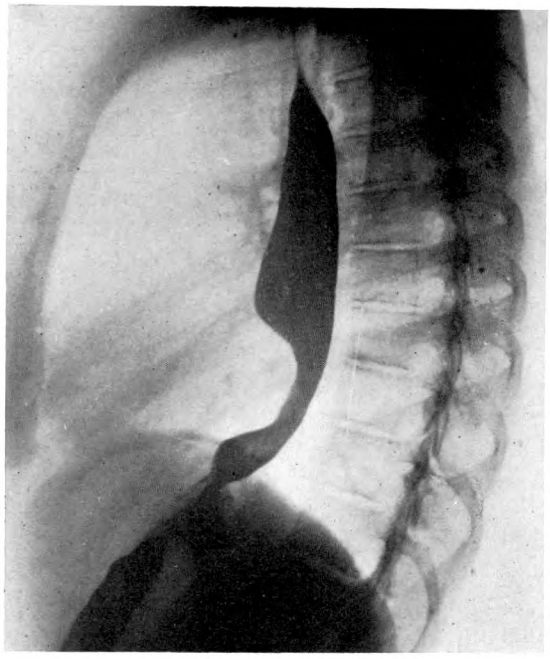


FIG. 1. Case 1. Preoperative esophagram.

vived 3 and 55 months, respectively; the remaining patients have survived 15, 12 and 3 years, the latter, our last case, having been operated upon in 1958.

REPORT OF CASES

CASE 1. A.L. (Case of Dr. W. L. Watson), a 46 year old white female, presented with a history of vomiting of 2 years' duration, dysphagia for a period of 1 year and vague substernal and left epigastric pain of unknown duration. A roentgenogram (Fig. 1) showed a $2\frac{1}{2}$ inch mass in the lower mediastinum with constriction of the distal esophagus. Esophagoscopy revealed a mass at 23.5 cm. originating from the anterior wall of the esophagus and protruding into the lumen, 4 cm. in transverse diameter and 2 cm. in anteroposterior diameter, attached by a stalk about 2 cm. wide and 5 cm. in length. On March 26, 1946, a left thoracotomy was performed and the esophageal tumor was resected. On July 11, 1947 she was re-admitted for re-evaluation because of ulcer symptoms. The stools were positive for occult blood. On February 15, 1954 roentgenograms showed operative deformity of the lower esophagus, sliding hiatal hernia and residual duodenal deformity. Later cholelithiasis was also demonstrated on cholecystograms. The patient is still alive (1962) without any evidence of disease as regards her esophageal tumor, which was diagnosed as myosarcoma by the Department of Pathology.

CASE II. B.L. (Thoracic Service case), a 58-year old white female, presented with a history of dysphagia of unknown duration, regurgitation of 4 months' duration and pain at the angle of the left scapula of 1 month's duration. Nausea and heartburn had been present for 4 months. A roentgenogram of the esophagus showed the lower end to be deviated to the left, with narrowing and loss of mucosal pattern of the distal and abdominal esophagus and involvement of the cardiac end of the stomach. There was a 4 cm. mass indenting the esophagus with scalloping posteriorly. Esophagoscopy revealed a mass at 32 cm. with fixation of the right lateral wall and erosion by the mediastinal mass. On May 28, 1946, a left thoracotomy and resection of the esophageal tumor were carried out. The tumor mass measured $14\times9\times7$ cm., was located medial to the aorta and was intimately associated with the esophagus and upper part of the stomach. It also extended into the right chest for several centimeters and below the diaphragm to the level of the second lumbar vertebra. It was entirely retropleural and was moderately adherent to the posterior parietes and mediastinum. The pathologic report was leiomyoscarcoma. On August 28, 1946, an exploratory laparotomy was performed because of liver enlargement. Biopsy showed metastatic myosarcoma. Gastrostomy was done for feeding purposes. She expired in another hospital in September, 1946, surviving 9 months after the onset of symptoms and 3 months after resection of the tumor.

CASE III. A.G. (Case of Dr. A. Brunschwig), a 58 year old white male, presented with a history of dysphagia, regurgitation and belching of 5 months' duration. Esophagraphy and esophagoscopy were not performed. On June 25, 1948, a left thoracotomy with resection of an esophageal tumor in the distal thoracic esophagus was accomplished. The tumor measured about 10 cm. in its greatest diameter, was well encapsulated, and appeared to be extraluminal. It was readily shelled out. The patient had recurrent dysphagia in October, 1950 and was re-admitted in January, 1951. On January 31, 1951 a left thoracotomy was again done

and the recurrent tumor was resected by means of esophagogastrectomy and esophagogastrostomy. A tumor mass made up of confluent nodules measuring approximately 6 cm. in diameter was found attached to the cardia of the stomach close to the junction of the esophagus and the fundus of the stomach. The mass appeared to arise from the intramural portion of the stomach wall in the region of the cardia. The pathologic diagnosis was leiomyosarcoma on both specimens. The patient expired 2 years after the second operation, having survived 5 years from the onset of symptoms and 4 years and 7 months following the first resection.

Case iv. E.G. (Case of Dr. W. L. Watson), a 54 year old white female, had been treated with roentgen rays for thyroid enlargement in England in 1918 and again in 1919. Roentgen therapy was again given in this country in 1936. In October, 1948 she was seen here with a history of dysphagia of 1 year's duration associated with pain in the throat radiating to the left neck and jaw. Four years previously she had had a right radical mastectomy for carcinoma. She also presented with a bilateral nodular goiter with tanning of the skin of the anterior and lateral neck. An esophagram (Fig. 2) showed a large bulky lesion involving the cervical esophagus, and esophagoscopy revealed a tumor mass just inside the cricopharyngeus. On December 7, 1948, a cervical esophagectomy, left lower neck dissection and left thyroid lobectomy were performed. The specimen revealed a fibrosarcoma of the cervical esophagus (Fig. 3 and 4) and carcinoma of the thyroid gland. It is felt that the tumor in the esophagus was radiation-induced as a result of the goiter therapy. Whether the carcinoma of the thyroid was existent prior to the irradiation is unknown, but this could also be radiation-induced. From April 6, 1949 through May 18, 1950, the patient had 9 operative procedures for esophagoplasty by means of a tube pedicle graft.[10] The patient is alive and well today, 13 years later. While in the hospital she also received 250 kv. therapy to the chin for a basal cell carcinoma. Thus, in this case there were 4 primary malignant tumors.[3]

Case v. E.M. (Case of Drs. G. T. Pack and T. R. Miller), a 58 year old white female, presented with a 12 month history of progressive dysphagia. An esophagram showed an enormous mass occupying the cervical and upper thoracic esophagus which appeared to be almost entirely within the lumen of the esophagus. Exploration of the neck disclosed an extensive neoplastic process which infiltrated almost the entire wall of the esophagus as far as could be palpated, up into the pharynx and downwards into the mediastinum. Laparotomy revealed no disease in the abdomen. Exploratory thoracotomy proved the tumor to be nonresectable as the arch of the aorta was involved as well as the origin of the innominate artery. Postoperatively, she was given 250 kv. therapy to the neck and chest until an air dose of 5,400 r was reached. Feeding was administered through a gastrostomy which was subsequently closed. Three months later she was taking a regular diet by mouth, and was without evidence of disease until 1956 when dysphagia recurred. She received a second course of radiation therapy elsewhere and was again improved. In 1958, she developed an epigastric mass with dys-

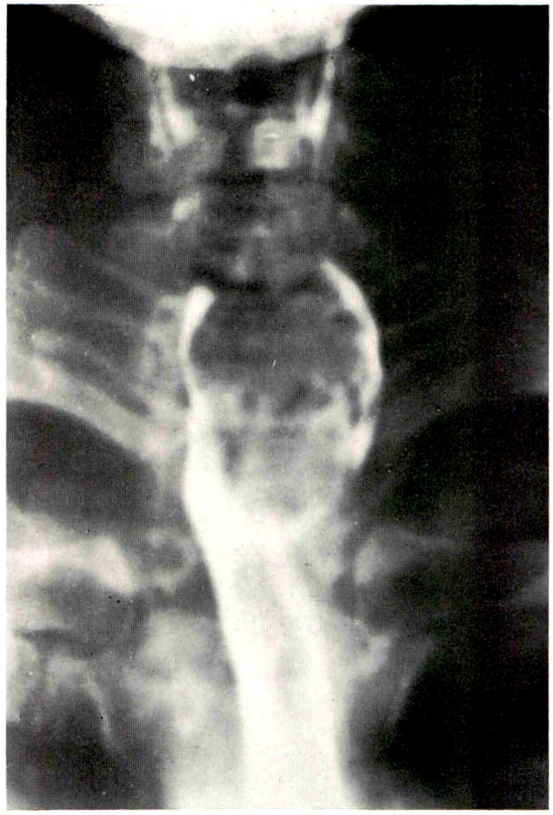


Fig. 2. Case iv. Esophagram showing tumor in the cervical esophagus (reproduced with permission of *Plast. & Reconstruct. Surg.* and Williams & Wilkins Co.[10]).



FIG. 3. Case IV. Gross specimen showing fibrosarcoma of the cervical esophagus (reproduced with permission of *Plast. & Reconstruct. Surg.* and Williams & Wilkins Co.[10]).

pepsia, weakness and loss of weight. Roentgen therapy was given to the abdomen, but in May, 1959 there was recurrence of the epigastric mass with abdominal pain. The disease progressed, and in November, 1959 an esophagram showed massive recurrence of the tumor in the cervical and upper thoracic esophagus with the presence of a tracheo-esophageal fistula. She was given radiation therapy to the chest (2,000 r air dose), together with mitamycin C, and also 5-fluorouracil, but she progressively went downhill and expired 11 years and 3 months after the onset of symptoms, and 11 years and 1 month after the start of radiation therapy. Biopsy of the tumor at the time of exploration revealed it to be a leiomyosarcoma.

CASE VI. J.P. (Thoracic Service case), a 50 year old Negro male, presented with dysphagia and pain in the upper thoracic vertebral area of 5 months' duration. There was also a history of swallowing lye at the age of 2 without the development of subsequent dysphagia. In addition, there were symptoms of lump in the throat, weakness, dyspnea and hoarseness. An esophagram showed a constricting lesion, annular in character, beginning about 4 cm.

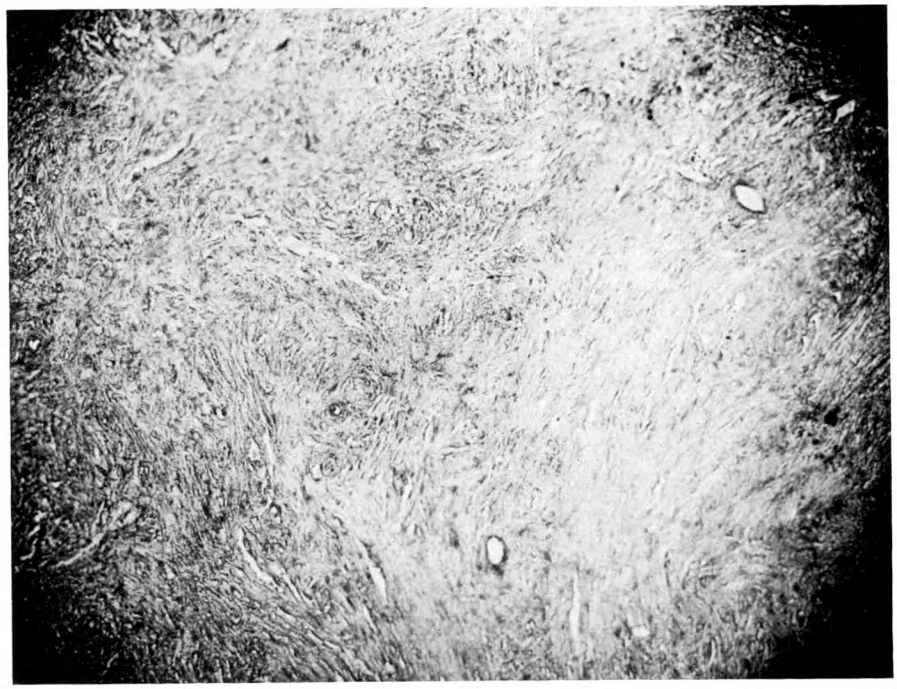


FIG. 4. Case IV. Microphotograph showing fibrosarcoma.

proximal to the aortic arch and extending downward for a length of about 8 cm., associated with mucosal destruction and anterior displacement of the esophagus. Rotational 250 kv. roentgen therapy was administered to the chest from May 12, 1955 to June 21, 1955 for a tissue dose of 3,200 r. By June 25 swallowing had improved, but subsequently he developed regurgitation, irregular narrowing of the tracheal air column, and on July 4, 1955 he was found to have a lesion of the right lower gingiva (Fig. 5) which on cautery excision was proved to be metastatic myosarcoma. The esophageal biopsy was previously reported as myosarcoma. Subsequently, he began to lose weight and a downhill course followed, with recurrence of the gingival tumor, vomiting, dyspnea, restlessness, coma and death 8 months after the onset of symptoms and slightly over 2 months following radiation therapy.

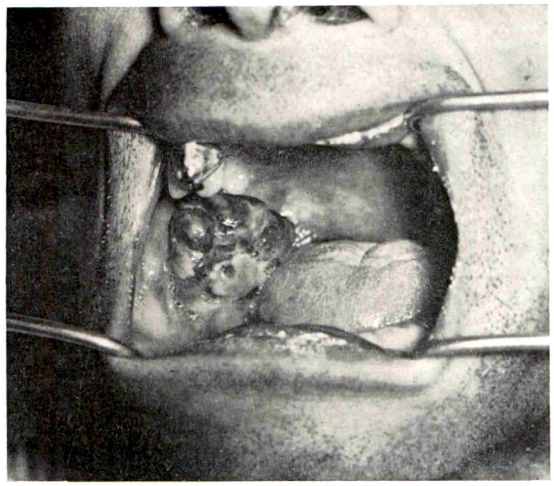


Fig. 5. Case vi. Photograph showing metastatic myosarcoma of the right lower gingiva.

Case vii. H.H. (Case of Dr. George T. Pack), a 56 year old white female, presented with retrosternal burning on swallowing hot or cold liquids of 6 months' duration (onset April, 1955). An exploratory thoracotomy was performed elsewhere and a leiomyosarcoma of the posterior mediastinum with lung metastases was found. Three courses of roentgen therapy were given (6,000 r in July, 1955; 4,000 r in April, 1956; and 3,000 r in August, 1956) with improvement after the first course of therapy. On admission she had an enlarged liver and subcutaneous nodules of the anterior abdominal wall (October, 1956) for which she received intravenous nitrogen mustard and radon seed

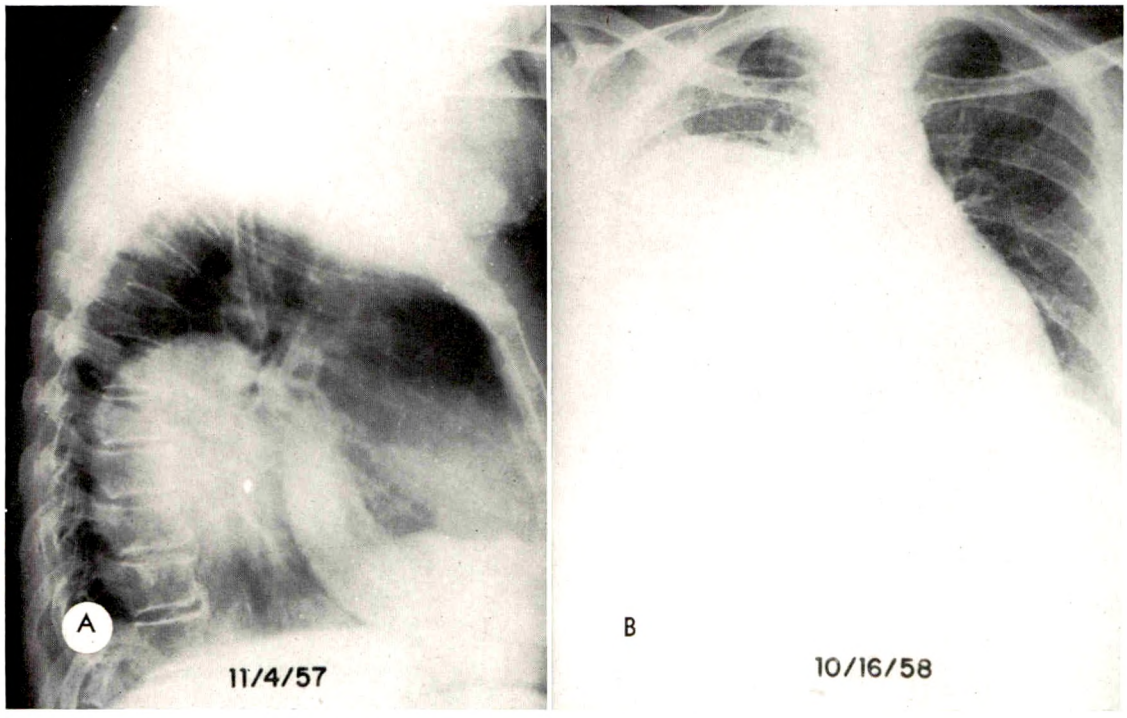


Fig. 6. Case viii. (*A* and *B*) Preoperative roentgenograms of the chest showing the tumor mass.

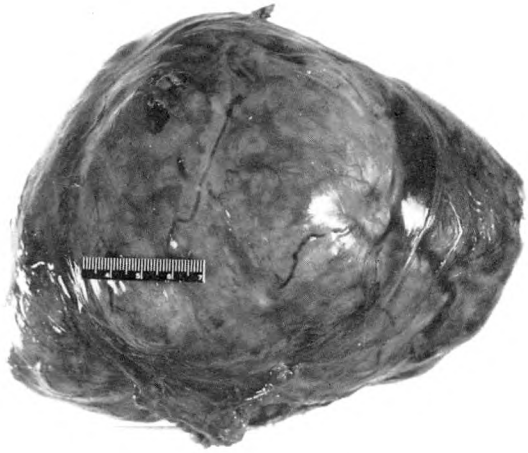


FIG. 7. Case VIII. Gross specimen showing leiomyosarcoma of the esophagus. (Stylet is seen through the resected segment of the esophagus.)

implantation in subcutaneous areas. Prior to this, radiation therapy was given for an epigastric mass and subcutaneous masses in the right and left thigh and left upper arm. A polypoid mass in the rectum was also proved by biopsy to be metastatic leiomyosarcoma. An esophagram revealed an extensive tumor of polypoid character in the mid-thoracic esophagus with paravertebral nodularity and extrinsic pressure on the lower thoracic eosphagus. There were also widespread parenchymal metastases of the lungs with apparent destruction of the right seventh rib posteriorly. Subsequently, she expired at home, 20 months after the onset of symptoms and 17 months after the start of the first course of radiation therapy.

CASE VIII. N.C. (Case of Dr. W. L. Watson), a 74 year old white female, presented with a history of dyspnea of 4 years' duration with recent increase in this symptom. There was no pain or dysphagia. Roentgenograms (Fig. 6, *A* and *B*) of the chest showed a large ovoid mass in the right hemithorax situated posteriorly and measuring about 4×6 inches. This was thought to be a mediastinal tumor. An esophagram was not made preoperatively. On December 4, 1958, a right thoracotomy incision was performed and a massive nodular tumor mass was found, measuring 22×15×13 cm. and weighing 1,790 gm. The tumor was apparently mediastinal in location, but arose from the distal esophagus which was transected on excision of the tumor (Fig. 7). The esophagus was re-approximated by end-to-end anastomosis. The postoperative course was relatively uneventful and she was discharged on the sixteenth postoperative day. She expired on March 18, 1962

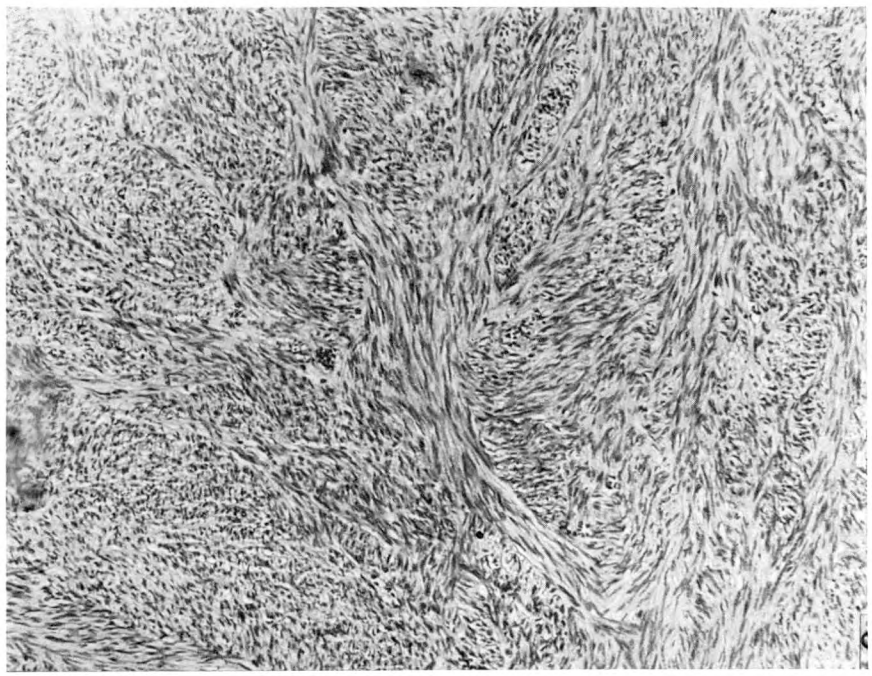


FIG. 8. Case VIII. Microphotograph showing leiomyosarcoma of the esophagus.

of other cause than sarcoma, surviving 39 months following the operation. The pathologic diagnosis was leiomyosarcoma of the esophagus (Fig. 8).

CONCLUSIONS

1. Sarcoma of the esophagus is a rare disease.

2. Of a series of 1,456 determinate cases of cancer of the esophagus, proved by biopsy or cytologic study, seen at Memorial Hospital from 1926 through 1961, there were 8 cases of sarcoma of the esophagus, or an incidence of 0.5 per cent.

3. The literature has been reviewed and some of the statistics from other papers are given.

4. Eight cases are reported in some detail, and the results of treatment and the survival time of these cases are summarized.

5. Surgical excision is the treatment of choice.

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RADIOACTIVE LYMPHANGIOGRAPHY AS A THERAPEUTIC ADJUNCT*

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LYMPHANGIOGRAPHY as advocated by Kinmonth in 1954 has recently gained in popularity as a diagnostic method. It soon became apparent that the lymphangiogram could provide certain information unobtainable previously. Our knowledge of the normal anatomy of the retroperitoneal lymphatic system has been increased and a better understanding of the route of lymph node metastases has been gained.

A joint investigation by the Urology Service and Department of Radiology of the Walter Reed General Hospital was initiated to determine the feasibility of utilizing lymphangiography as a therapeutic procedure. This study was stimulated primarily in an attempt to improve the survival rate of patients with testis tumors. The 5 year statistics in this group are far from satisfactory. The therapeutic approaches in the past have been altered in an attempt to improve the survival rates, but these have met with only moderate success.

The germinal tumors, comprising 96.5 per cent of testis tumors, can be divided into 4 basic patterns: (1) seminoma, (2) embryonal carcinoma, (3) teratoma, adult and immature, and (4) choriocarcinoma. The seminomas comprise the largest single group and are extremely radiosensitive, yielding a 5 year survival rate of 92 per cent with orchiectomy and radiation therapy. The choriocarcinoma is rare, 1.8 per cent of the total, and has an extremely poor prognosis. The embryonal carcinoma and teratoma account for the bulk of the tumors seen, 59.7 per cent, and provide the most controversy in management. The survival rates of these patients vary with the type of treatment, and it is toward this group that most of our efforts in seeking an improved therapeutic approach has been directed. Current practice for this group at Walter Reed is to perform a bilateral transperitoneal retroperitoneal lymphadenectomy following the orchiectomy and give external radiation therapy only if positive lymph nodes are found. In a survey of 510 cases of testis tumors reported from this institution by Patton and Mallis[1] in 1959, there were 51 patients who survived 5 years following the removal of positive retroperitoneal lymph nodes and of even greater interest is the group of 192 patients with negative lymph nodes, of whom 26 or 13½ per cent subsequently died of their tumor. Several explanations for this have been proposed: (1) there were undetected distant metastases prior to surgery; (2) the lymphadenectomy was inadequate; (3) there was contralateral involvement of retroperitoneal lymph nodes (in this series prior to 1954 unilateral lymph node dissections were performed); and (4) microscopic metastases were missed in the sampling of the specimen by the pathologist.

Lymphangiography has demonstrated that it is almost impossible to surgically remove all of the retroperitoneal lymphatic tissue. In all instances studied either one or more lymph nodes remained following the dissection, and for the most part they were located in the retrocaval area or just above the level of the renal pedicles. From a surgical standpoint the retrocaval region provides the greatest difficulty in dissection. Occasional lymph nodes are left behind in spite of elevation and rotation of the vena cava which is performed to facilitate the removal of all possible lymphatic tissue. In addition, it has been noted in all instances that there is lymphatic spillage early in the

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operation when the lymphatics are divided in the region of the renal pedicles. This occurs even though the tissues are meticulously divided between ligatures. The danger of spreading viable tumor cells is, therefore, inevitable.

It is apparent that the survival rates should be improved by any form of therapy which will increase the adequacy of the lymph node dissection or produce tumor sterilization of the lymphatics prior to their surgical excision. The benefit of complete extirpation of the lymph nodes is obvious. The tumor sterilization of the lymphatics has a two-fold purpose: (1) it will prevent the spillage of viable tumor cells during the dissection, and (2) if lymph node tissue is left behind, it will be less likely to contain viable tumor cells. With this goal in mind, a study was started to evaluate the feasibility of combining radioactive isotopes with ethiodol. This procedure, of course, would have its limitations. The isotope, together with the ethiodol, will bypass a large tumor mass and will not invade a lymph node completely replaced by tumor. Therefore, it will have no effect upon them. Distant metastases would likewise be unaffected. In those patients with inoperable lymph node involvement or distant metastases, curative treatment of any type is unsatisfactory. Our efforts were directed primarily to the group of patients with "negative" or microscopically positive lymph nodes.

METHOD

The first problem was to select a suitable isotope which would have the following properties: (1) it must be homogeneous in ethiodol; (2) it must stay within the lymphatic system; (3) it must be distributed uniformly in the lymph nodes; (4) it must be primarily a beta emitter; and (5) the degradation products must be innocuous. If the particle size were too large, the isotope would be filtered out by the first lymph nodes encountered, and if it were too small, it would leak through the walls of the vessels. The first isotope selected for study was Au^{198}. It was used in scanning doses, 50 and 100 μc, which were mixed with the standard ethiodol and given in a routine manner. Scans were then obtained of the inguinal and retroperitoneal areas. There was marked diffusion of Au^{198} out of the lymphatic vessels into the soft tissues, especially in the leg. Colloidal Au^{198} was, therefore, discarded.



Fig. 1. Lymphangiogram obtained with 150 μc I^{131} ethiodol.

An almost ideal substance resulted when the stable iodine content of ethiodol was converted to I^{131}.* Initially, scanning doses in the range of 100–200 μc were utilized during routine lymphangiographies. As would be expected, subsequent magna scans demonstrated that the material remained within the lymphatic system. There was no measurable uptake of the material in the liver, kidneys, spleen (Fig. 1) or thyroid. Several repeat studies produced consistent results. The I^{131} content was then increased, and the material utilized during the remainder of the study contained 2 mc/cc. of ethiodol.

Perfect placement of the intralymphatic

* This was performed at Oak Ridge and supplied to us through the courtesy of E. Fougera & Co.



FIG. 2. Roentgenogram after injection of a small amount of standard ethiodol to ascertain position of the cannula.

cannula was mandatory during injection of I^{131} ethiodol. A leak would result in a radiation hazard to both the patient and the physician. It would also complicate the calculation of the dose administered by obscuring the exact volume delivered into the lymphatic system. A small amount of standard ethiodol was injected initially and a roentgenogram was obtained of the foot to be certain of the position of the cannula (Fig. 2). I^{131} ethiodol injection was started only after these roentgenograms were reviewed and good visualization of the lymphatic vessels of the foot was demonstrated.

In order to minimize the potential hazard as well as to recover the retroperitoneal lymph nodes for study, it was decided to utilize terminal carcinoma patients in this stage of the investigation. Only those patients with relatively normal retroperitoneal lymph nodes were selected. This, of course, was not always possible. Total doses of I^{131} ethiodol per patient varied from 4–19 mc. Following lymphangiography serial complete blood cell counts, platelet counts, blood and urine assays, as well as thyroid scans were obtained. In several patients the thyroid was blocked with Lugol's solution prior to the procedure and the results will be noted later. At postmortem examination the entire retroperitoneal area was removed en-bloc, placed in formalin, and dissected on the following day with the aid of roentgenography and fluoroscopy. Representative tissue was also removed from the lungs, liver, kidneys, and spleen and found to have no significant increase in activity above background. Representative lymph nodes from selected levels were counted against a known I^{131} standard in a Nuclear Chicago well counter. The I^{131} count at the T_0 (time of injection) was calculated. The absorbed dose in rads was calculated utilizing only the beta emissions. The contribution from gamma emissions was thought to be insignificant because of the small size of the lymph nodes. These lymph nodes were then examined by the pathologist for radiation effect.

DISCUSSION

The following formula was utilized to calculate the dosage delivered to the individual lymph nodes removed:

Dose (in beta rads to total decay *in vivo*) $=73.8\times$concentration (μc/gram) $\times 0.187$ (E_β for I^{131}) $\times T_{eff.}$ (effective half-life).

Figures 3 to 6 represent the results obtained. Two possible sources of error are present which could appreciably alter the results obtained. These consist of the effective half-life of I^{131} and the estimation of the weight of the lymph nodes. It was discovered early in the study that isolation of the freshly removed lymph node was impractical. Tissue juices together with I^{131} ethiodol were expressed from the lymph node by the manipulation necessary to isolate it from all the surrounding fat. This yielded a low assay of radioactivity. There-

fore, it was decided to fix all tissues in formalin for 24 hours, following which the isolation of the lymph node was easier and less traumatic. In the majority of patients studied, the lymph nodes were embedded

Total Dose Administered—8.7 mc

Lymph Node	Location	Estimated Weight	μcT_o	Beta rad Dose
1	Rt. external iliac	0.75 gm.	0.39	15,350
2	Rt. common iliac	0.5 gm.	9.65	1,600
3	Lt. external iliac	0.5 gm.	95.00	15,750
4	Lt. common iliac	1.0 gm.	56.10	4,650
5	Rt. pericaval	0.5 gm.	22.80	3,800
6	Lt. periaortic	0.75 gm.	43.00	4,750
7	Lt. periaortic	0.5 gm.	8.90	1,500

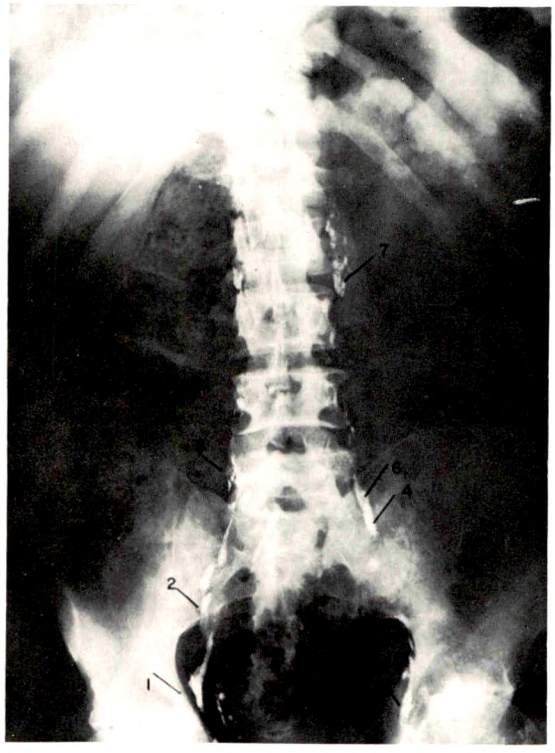


Fig. 3. R.W. was a 54 year old male with far advanced squamous cell carcinoma of the lung. There was no clinical evidence of retroperitoneal involvement. The patient expired 35 days following radioactive lymphangiography. Total dose of I^{131} ethiodol was 8.7 mc.

Total Dose Administered—5.04 mc
($\frac{2}{3}$ Lt., $\frac{1}{3}$ Rt.)

Lymph Node	Location	Estimated Weight	μcT_o	Beta rad Dose
1	Lt. external iliac	0.5 gm.	37.6	6,200
2	Rt. iliac	1.0 gm.	24.0	2,000
3	Rt. pericaval (contained tumor?)	0.5 gm.	16.6	2,750

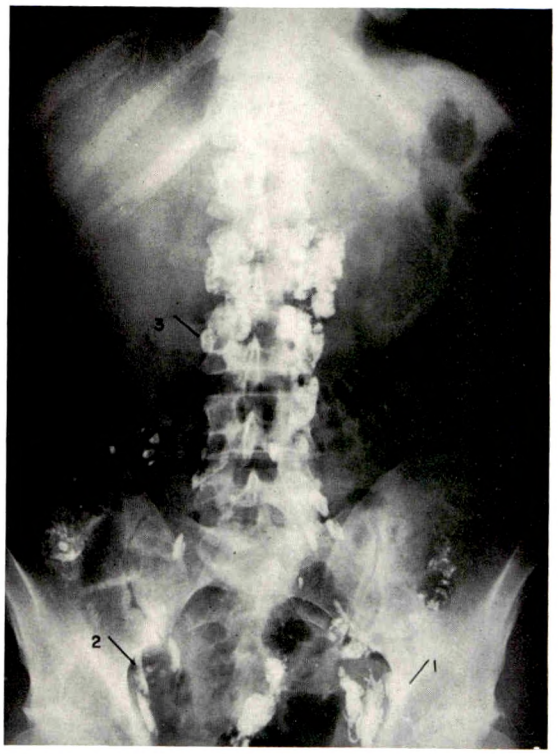


Fig. 4. B.B. was a 46 year old male with extensive supraclavicular and mediastinal metastases from an adenocarcinoma of the lung. Lymphangiogram demonstrated metastatic tumor in the periaortic lymph nodes. The patient expired 43 days after radioactive lymphangiography. In this patient, difficulty with position of the right lymphatic cannula allowed more material to enter the left side. Total dose of I^{131} ethiodol was 5.04 mc but two-thirds of it was injected on the left and only one-third on the right.

in a considerable amount of fibro-fatty tissue and accurate isolation of the lymph node was still impractical. All dissections were performed under fluoroscopic control

Total Dose Administered—19.6 mc

Lymph Node	Location	Estimated Weight	μcT_0	Beta rad Dose
1	Lt. inguinal	1.0 gm.	112	9,300
2	Rt. inguinal	1.0 gm.	113	9,400
3	Lt. common iliac	1.0 gm.	66	5,500
4	Rt. common iliac	1.0 gm.	53	4,400
5	Lt. periaortic	0.5 gm.	69	11,400
6	Lt. periaortic	0.5 gm.	45	7,450

but considerable manipulation was necessary, with its inherent risk of expressing ethiodol, or lymph nodes inadvertently being transected. It was finally decided to estimate the weight of the lymph node by comparing its roentgenogram with roentgenograms of lymph nodes of known weight.

The effective half-life of I^{131} ethiodol was estimated to be 6 days. It is based upon the radioactive assays of serial blood and urine specimens in selected patients. These studies were performed primarily to evaluate the rate of breakdown and the release of ethiodol from the lymph nodes and to gain insight into the phyisology of ethiodol excretion. Arrangements are presently underway to determine the exact effective half-life by utilization of a human whole body counter.

Prior to the utilization of I^{131} ethiodol, it was discovered that routine lymphangiography effectively blocked oral I^{131} uptake by the thyroid within one week. This led to the assumption that sufficient breakdown of ethiodol occurred within the lymphatic system to release iodides into the blood stream which effectively saturated the thyroid gland and halted its iodide uptake. In an attempt to augment this inherent blocking mechanism and prevent I^{131} uptake by the thyroid, several patients re-

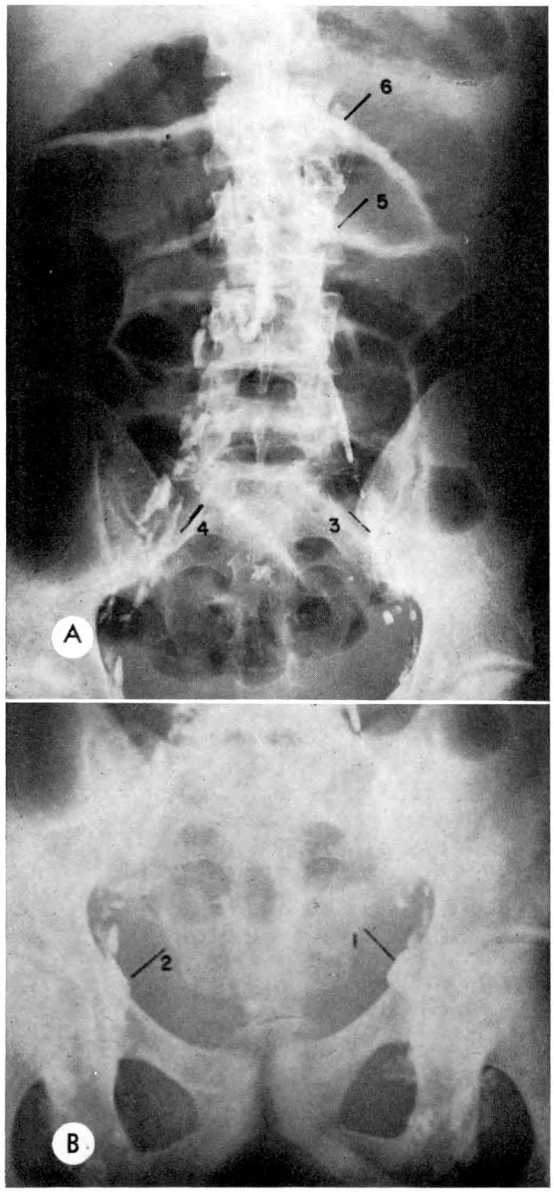


FIG. 5. (*A* and *B*) K.F. was a 21 year old male with lymphosarcoma. A rapid downhill course manifested by severe platelet count depression, lack of response to chemotherapy, and progressive lower extremity edema followed the diagnosis in January, 1962. Radioactive lymphangiography was followed by a short remission characterized by a return of the platelet count to normal levels and disappearance of edema in the lower extremities. He became ambulatory, whereas he was bedridden prior to this study. The patient expired 35 days following radioactive lymphangiography. Total dose of I^{131} ethiodol was 19.6 mc. Postmortem examination revealed that the retroperitoneal lymph nodes were considerably smaller than the lymph nodes elsewhere.

ceived Lugol's solution, starting several days before and continuing 5 to 7 days after lymphangiography. Further proof of efficient thyroid blocking is demonstrated by the lack of magna scan activity in the region of the thyroid in all of the patients tested.

Serial blood studies beginning immediately following I^{131} ethiodol administration revealed that almost all radioactivity was contained in the plasma or serum fraction and was not ether extractible as was undegraded I^{131} ethiodol. This led to the further assumption that ethiodol was broken down to iodine or iodides prior to its release from the lymphatic system.

With the iodine uptake of the thyroid gland effectively blocked, the majority of free iodine or iodides, released into the systemic circulation, should be excreted by the kidney. For the purpose of this study, the iodine excretion in feces and perspiration was neglected and only serial blood and urine radioactivity was monitored. The individual specimen assays were then calculated in terms of the percentage of the dose administered so that all of the patient studies would be on a comparable basis. Several reproducible factors were observed. The peak in activity of both urine and blood occurred between 2 and 6 days after I^{131} ethiodol administration. Both the urine and the blood peaks were low, ranging from 0.4 per cent to 0.5 per cent of the administered dose in the total blood volume and ranging from 2 per cent to 2.5 per cent in the 24 hour urine collection. Typical urine and blood excretion results are illustrated in Figures 7 and 8. These findings indicate that I^{131} ethiodol has a long biologic half-life within the lymphatic system. It is degraded to free iodine and iodide and released into the systemic circulation in only small amounts. By adding Lugol's solution, the inherent thyroid blocking capacity of ethiodol is augmented and protein bound iodine 131 formation is prevented. This allows rapid I^{131} excretion in the urine, thereby protecting the thyroid gland and the body as a whole from unnecessary radiation.

Total Dose Administered—3.89 mc

Lymph Node	Location	Estimated Weight	μcT_o	Beta rad Dose
1	Rt. common iliac	1.0 gm.	24	2,000
2	Lt. common iliac	0.5 gm.	14	2,300
3	Lt. periaortic	1.0 gm.	24	2,000

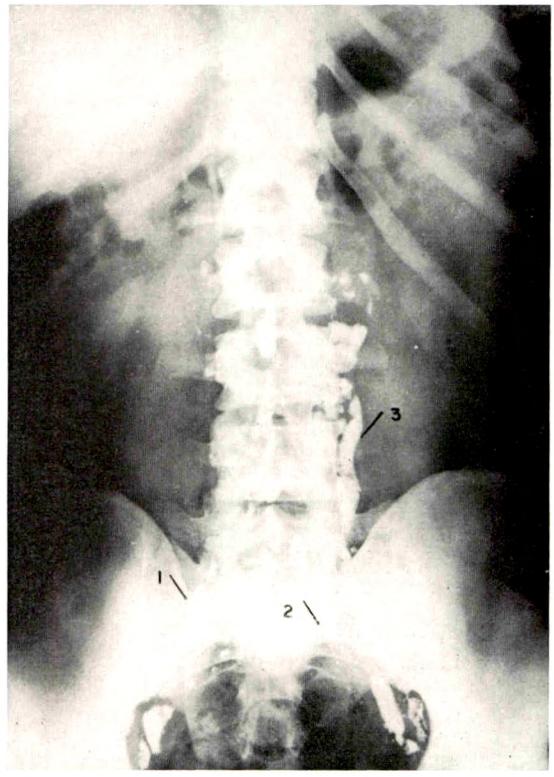


Fig. 6. L.G. is a 39 year old male with an embryonal carcinoma of the left testis. Five days prior to transperitoneal retroperitoneal lymphadenectomy, radioactive lymphangiography delivering a total dose of 3.89 mc was performed. This was done mainly to evaluate the distribution and dose delivered to individual lymph nodes. Two lymph nodes contained microscopic tumor. The patient is alive and well and had no adverse side effects from this procedure.

In addition to the danger of radiation from degradation products, there is the danger that I^{131} ethiodol will reach other tissues, primarily the lungs, in sufficient quantity to be harmful. There are two ways in which this may occur: (1) "overflow,"

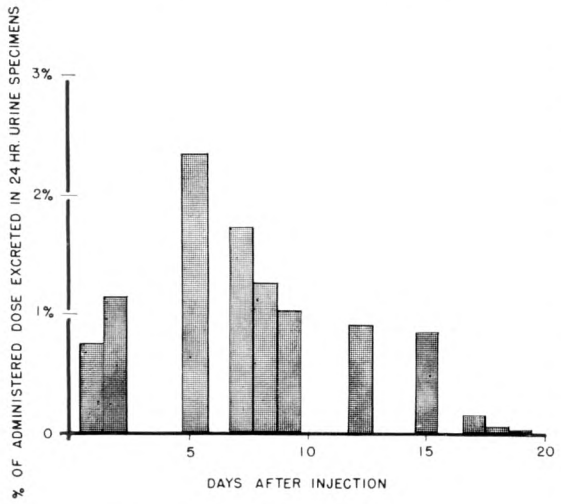


FIG. 7. Urine excretion of I^{131} ethiodol (administered dose 22.9 mc).

or ethiodol that passes through the lymphatic vessels into the thoracic duct; and (2) direct lymphatic-venous anastomosis in the retroperitoneal area (as demonstrated by Shanbrom and Zheutlin[2] and corroborated by our clinical investigation of lymphangiography in this institution). It is possible to control the amount of ethiodol entering the thoracic duct by careful technique. Fluoroscopic localization of the ethiodol is performed during the procedure which is terminated whenever ethiodol reaches the thoracic duct. The amount of ethiodol entering the venous circulation and thence the lungs as a result of direct lymphatic-venous anastomosis is unpredictable and uncontrollable. In all of the patients studied, radioactivity was noted over the lung fields by magna scan, but postmortem examination of the lungs failed to show measurable radioactivity. It was, therefore, concluded that this was not a significant hazard. Failure to monitor the ascent of ethiodol may allow an excessive amount of it to reach the lungs with its potential radiation hazard. In addition, it should be noted again that examination post mortem of other viscera such as the liver, kidneys, spleen, and thyroid failed to record measurable radioactivity. Serial complete blood cell counts and platelet counts performed bi-weekly for several weeks demonstrated no change from the pre-test levels in any of the patients studied. This is accepted as conclusive evidence that the hematopoietic system is unaffected by this procedure.

It was found that 9–12 cc. of ethiodol was necessary to adequately fill the retroperitoneal lymphatic system without appreciably filling the thoracic duct. In every case of I^{131} ethiodol injection, the lymphatic cannula fit snugly and no leakage was tolerated. I^{131} ethiodol assaying as high as 10 mc/cc. is now available, and it would be conceivable to deliver a maximum dose of 120 mc. The optimum dose, however, must be calculated to allow these patients to undergo a surgical procedure, usually lymphadenectomy, without hazard to the operating room personnel. In addition, the time interval between lymphangiography and surgery must be consistent with good cancer technique. A long interval could not be allowed. According to the Atomic Energy Commission recommendations, a maximum total assay of 5 mc is permissible for laparotomy without radiation precautions.

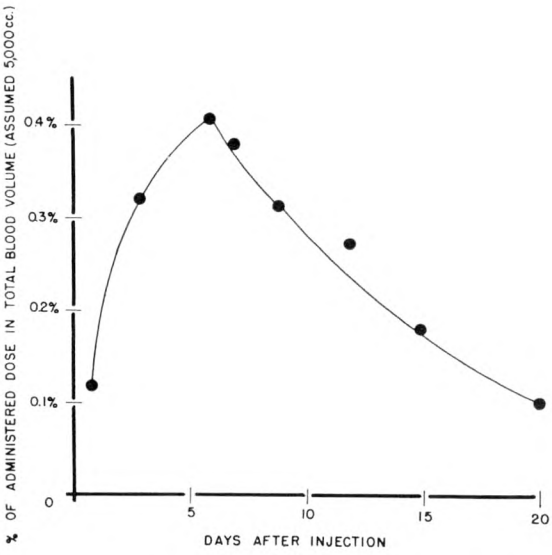


FIG. 8. Blood excretion of I^{131} ethiodol (administered dose 22.9 mc).

The optimum total dose selected consistent with these principles is 18–24 mc, using 2 mc/cc. of I^{131} ethiodol. Interpolating the possible total beta rad dose on the basis of the previously described formula, in the patient illustrated in Figure 3 it would be 30,700 and 5,000 rads respectively for the maximum and minimum lymph nodes.

The time interval may be varied slightly depending on the surgeon's preference. The fraction of the total rad dose administered is calculated by the following formula: $D_\beta(t) = 73.8(1\text{-}E^{-(0.693)\,t/T_{eff.}})c\overline{E}_\beta T_{eff.}$ If 28 days elapsed between injection and surgery, a reduction of only 4 per cent would result in the calculated total decay rad dosage. A minimum interval of 2 weeks is necessary to permit surgery without radiation precautions or hazard to the operating team. The reduction in the rad dosage for this time interval would be 19 per cent. These time intervals would constitute the recommended maximum and minimum.

In those patients who would not require a surgical procedure, the total dose administered could be higher. If the dose exceeds a total of 30 mc, isolation technique would be necessary. It might be possible to increase the total effective dose by repeating a radioactive lymphangiography 2 weeks following the first injection. If a lymphadenectomy were then to be performed 4 weeks after the initial injection, those lymph nodes not removed would contain twice the original calculated dose to total decay.

The final test of this technique rests upon the histologic evaluation of the radiation effect in the lymph node studies. Prior to discussing the pathology, one point needs clarification. Can all the retroperitoneal lymph nodes be filled with ethiodol? Granulomatous reaction secondary to ethiodol was noted in all of the retroperitoneal lymph nodes found at postmortem examination. Further proof is obtained from the retroperitoneal lymphadenectomies in which ethiodol filled lymph nodes remain in spite of what appears to be a complete extirpation of all lymph node tissue. The pathologist reports numerically less total lymph node tissue than is accounted for on a flat roentgenogram after lymphangiography. This is sufficient inferential evidence that all of the retroperitoneal lymph nodes can be filled with I^{131} ethiodol.

This histologic response to ethiodol must be differentiated from the radiation effect. Those lymph nodes invaded by ethiodol demonstrate consistent and characteristic reaction with preservation of the over-all shape and form of the lymph node. Large fat droplets appear first in the subcapsular and then in the medullary sinuses. A foreign body reaction to the fat is produced with the appearance of large histiocytes and multinucleated giant cells. In contradistinction, those lymph nodes subjected to I^{131} ethiodol show characteristic changes noted in other types of irradiation. After a variable latency period, there is pyknosis, loss of cytoplasm, and dropping out of lymphocytes. This is accompanied by diminishing mitoses and disappearance of the germinal centers. If the dose of radiation delivered is sufficient, as illustrated in the patients in Figures 3 and 5, *A* and *B*, the architecture of the lymph node is present in only a skeletonized form. Vascular changes secondary to radiation are likewise present with the swelling, fraying, and degeneration of the collagen and smooth muscles in the walls and hyperplasia and swelling of the endothelium. Occlusion of the lumen and/or thrombosis may result (Fig. 3). Tumor cells may also exhibit radiation effect as illustrated in the patient shown in Figure 5. In this instance a very radiosensitive tumor was present. Radiation effect outside the lymph node is limited to a distance of one low power field (0.5 mm.), and it is in keeping with the short, penetrating ability of the beta radiation employed. The lack of response in the surrounding tissue confers an added safety feature to this procedure. The dose delivered may be high without danger of

damage to the nearby vital organs and subsequent external irradiation will not be contraindicated or affected by the amount of radiation delivered by lymphangiography.

The histologic response of the lymph nodes studied in this series varied from no effect to complete destruction. The total dose delivered reached the recommended therapeutic range in only one patient and he demonstrated a good response. In the other patients, the primary concern was the distribution and fate of I^{131} ethiodol. Current investigation, in which therapeutic doses are being delivered, will yield more information concerning the histologic response of the normal lymph node and the metastatic tumor to I^{131} ethiodol.

APPLICATIONS

The results obtained during this investigation have been very encouraging. No morbidity other than that occasionally noted with routine lymphangiography was encountered and, therefore, there are no contraindications to the procedure. Radioactive lymphangiography may be applicable in the case of any tumor which routinely metastasizes to the inguinal or retroperitoneal lymph nodes. This would include almost all genitourinary tract tumors. The I^{131} ethiodol could be given prior to lymphadenectomy in penile and testicular carcinomas and would irradiate those lymph nodes above the common iliacs in carcinomas of the bladder. It might prove beneficial in cases of renal carcinomas by treating the regional lymph nodes, many of which may be left behind after radical nephrectomy. Should the surgeon desire to operate without delay in patients with renal tumors, lymphangiography could be performed postoperatively. For those who would wait 2 weeks, radioactive lymphangiography may sterilize the regional lymph nodes and diminish the possibility of seeding viable tumor cells during surgery. This technique does not appear to be applicable to cases of prostatic carcinoma except in specific instances.

The squamous cell carcinoma of the cervix cases provide another large group which may be potentially benefited by this technique. If lymphadenectomy is performed, it is usually limited to the pelvis. However, early positive periaortic lymph nodes are occasionally found. Injection of I^{131} ethiodol would treat those lymph nodes above the level of the lymphadenectomy and increase the scope of the treatment without any increase in morbidity. Another potential group of candidates are those patients with abdominal lymphomas. As illustrated by the patient in Figure 5, *A* and *B*, the involved retroperitoneal lymph nodes are definitely improved. This mode of therapy may not displace the well-accepted external irradiation, but it could be beneficial as an adjunct or as palliation in those patients who could not tolerate further systemic effects of radiation or chemotherapy.

SUMMARY

The stable iodine content of ethiodol can be converted to I^{131}, and the intralymphatic injection of this material can be used as a therapeutic adjunct in the treatment of malignancies which metastasize to the inguinal or retroperitoneal lymph nodes. This study has demonstrated that a substantial, relatively uniform assay of radioactivity can be delivered to the retroperitoneal lymph nodes. Furthermore, these lymph nodes exhibit significant histologic effects of radiation. There were no complications or adverse side effects encountered. Investigation demonstrated no uptake of I^{131} by the thyroid, no effect on the hematopoietic system, and rapid renal excretion of iodine and iodides in very small amounts. The I^{131} ethiodol was noted to have a long biologic half-life in the lymphatic system. All other tissues examined failed to demonstrate significant radioactivity above background. It is proposed that this technique is applicable in almost all cases of genitourinary tumors but primarily those of the penis and testis, squamous cell carcinoma of the cervix, abdominal lymphomas, or any other

malignancy metastasizing to the inguinal or retroperitoneal lymph nodes. This procedure is now undergoing clinical trial and will be the subject of a subsequent report.

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THE MANAGEMENT OF CARCINOMA OF THE BLADDER USING SUPERVOLTAGE MODALITIES*

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IN THE past, orthovoltage techniques for the management of carcinoma of the urinary bladder have been discouraging not only because of the poor patient tolerance of the dosages utilized, but because of the poor tumor control. Radiation therapy using these techniques has yielded 5 year survivals in the range of only 5 per cent to 7 per cent.

The behavior and management of carcinoma of the bladder depend on many things. Important among these is host resistance. Host resistance can be enhanced by the control of pain and other distressing symptoms. Other factors include the susceptibility of the tumor to radiation and its biologic aggressiveness as well as the grading of the tumor and the degree of infiltration of the various layers of the bladder wall.

Jewett[6,7] and later Marshall and Whitmore[8,11] correlated the results of treatment with the degree of invasion of the bladder wall. It was apparent that surgical treatment of high grade, deeply infiltrating lesions, regardless of technique, yielded 5 year survivals only in the range of 15 per cent. The prognostic value of the degree of bladder wall penetration, stressed by the above authors, cannot be ignored in the evaluation of any series treated either by surgery or by radiation therapy. However, Marshall's dual classification is a surgical and not a clinical classification. It does not allow for grouping of all patients treated by radiation therapy.

In 1959, Rubin and Buran[10] presented a classification which would be meaningful for radiation therapists. The factors to be regarded were divided into primary, relating to the prognosis and evolution of the disease in the average patient, and secondary, relating to the successful treatment of a specific individual.

Three groups of patients emerged from such a classification. Group 1 (superficial stage—low grade) would include papillomas that show evidence of invasion and atypical features histologically (Stages 0, A, B1 and Grades I and II). Group 2 (deep stage—high grade) would include the cases with deep anatomic invasion or with an advanced histologic grade (Stage B2, C and Grades III, IV and V). It seemed wise to include all tumors with evidences of biologic aggression by virtue of deep stage or high grade in this group, particularly since the philosophy of treatment is similar.

Once definite extension of the infiltrative process to the surrounding perivesical tissues was noted, the cases were staged as metastatic and high grade, Group 3 (Stage D and Grades III, IV and V).

Obviously, the most accurate clinical staging is accomplished when there is a close working cooperation between the radiotherapist and the urologist.

CASE MATERIAL

Forty-nine patients with carcinoma of the urinary bladder were selected for treatment since 1948. The histologic classification was made with great care, the grading of the lesions being classified by Broders' criteria. There were 41 patients with a transitional cell carcinoma of the bladder, 7 patients with an anaplastic carcinoma of the bladder and one patient with a squamous cell carcinoma involving the bladder. The ages of these patients ranged from 36 to 86 years with a median age of 64 years. There were 12 females and 37 males; 46

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patients were white and the remaining 3 were Negroes.

Hematuria was the prevailing complaint in 45 of the patients. Dysuria was found in 13 of the patients, pain in 6, frequency in 5, repeated bouts of cystitis in 2 and incontinence in one.

Eighteen of the patients had transurethral surgery in the past; 15 of the patients had suprapubic surgery. A radium placement or implantation had been done in 2 patients in the past, whereas 2 had a history of a radon seed implantation. Seven of the patients in the series had been treated previously by orthovoltage techniques.

The past history of 8 patients revealed that there were previous malignancies in other locations. One patient had carcinoma involving the buccal mucosa, one patient had been treated with radiation for carcinoma of the cervix, 2 patients for carcinoma of the sigmoid (surgical excision), one patient for carcinoma of the ureter (surgical excision), one patient for carcinoma of the prostate (surgically removed), one for seminoma (treated with surgery and external radiation therapy modalities, the external radiation therapy being given to the lymph nodes draining the left testicle), and one patient for carcinoma of the breast (treated by radical surgery).

The patient with the history of seminoma had received several courses of radiation therapy following the surgical excision of the involved testis, the last course of external radiation therapy being given in 1942 with the treatment portals directed toward the pelvis, some 13 years prior to the development of his carcinoma of the bladder.

The patient with the carcinoma of the cervix had received radiation therapy 4 years prior to the development of the carcinoma of the bladder. Careful examination of the sections eliminated the possibility of the bladder lesion being related to the carcinoma of the cervix. Naturally, it would be interesting to speculate on the possibility of radiation as the cause of the bladder carcinoma in these 2 cases.

Five of the patients had an immediate past history of having received 5-fluorouracil therapy.

METHOD

The two million volt Van de Graaff generator was utilized as the means for external radiation therapy in the management of these lesions in preference to interstitial or intracavitary irradiation. In planning the radiation therapy, the aim was to treat the entire empty bladder. The decision in this regard was based on the work by Baker *et al.*[1,2] demonstrating circumferential lymphatic spread of cancer cells along the muscle wall as well as a high incidence of lymph node involvement in the perivesical structures. It was obvious from their work that these findings would necessitate a more radical approach to the treatment of bladder carcinoma regardless of whether surgery or radiation therapy was utilized. The treatment was planned so that 6,000 rads would be delivered to the entire bladder in 6 elapsed weeks.

When there was no evidence of extravesical extension of the tumor as determined by rectal and bimanual examination, only the bladder and a small surrounding margin of tissue were treated (a three portal technique). However, when extravesical extension was palpable, larger fields were used so as to include within the treated volume the entire bladder as well as the extravesical tissues and the pelvic lymph nodes (four portal technique). The fields in the four portal technique were also extended to include the lymph nodes at the junction of the external-internal iliac veins and the prostate. The portals of entry of the external roentgen-ray beam ranged in size from 80 sq. cm. to 150 sq. cm.

The accuracy of the direction of the beam was checked routinely with the patient in the treatment position by localization air-contrast roentgenograms of the bladder. On each patient, a volume distribution of the dosage was made after localization of the bladder by cystogram. The volume being irradiated was limited as much as possible,

consistent with the stage of the disease. Palliative cases were treated either by the use of a single anterior field, or by parallel opposed fields. All patients had cystoscopic examinations at regular intervals following the completion of radiation therapy.

Eight patients received a course of radiation therapy utilizing the supervoltage modality in a palliative manner, whereas 41 patients were treated in a definitive manner. Of the 49 patients treated, 28 were irradiated utilizing a three portal technique and 9 with a four portal technique. In the remaining 12 patients either a single anterior portal or parallel opposed anteroposterior portals were employed.

In the 8 patients who received supervoltage radiation therapy for palliation, the median tumor dose was 2,200 rads. The time in which the treatment was given ranged from 3 to 27 days with a median of 11 elapsed days. In the 41 patients treated in a definitive manner, the median tumor dose was 6,300 rads. The elapsed time in which this was delivered ranged from 27 to 94 days with a median of 56 elapsed days.

RESULTS

In the group treated palliatively, one patient is living with residual tumor within the pelvis, whereas 6 are dead from their malignancy. The median survival period following radiation therapy was 19 days.

Of the 41 patients treated definitively, 17 are alive. All have no evidence of recurrent malignancy. Twenty-four patients who were treated definitively have died, 21 with recurrent or metastatic malignancy; 9 of these had local persistence of the disease involving the bladder, whereas death was due in 12 instances to metastatic disease but without evidence of local persistence or recurrence. Three patients died without evidence of malignancy, the cause of death being coronary occlusion, sepsis and pulmonary edema, respectively. The median survival period for the 21 patients who died was 9 months after the completion of the radiation therapy with an over-all median survival period for the group treated definitively of 12 months.

Of the 5 patients who received 5-fluorouracil immediately prior to the radiation therapy, one is alive and the other 4 are dead. It was our impression that the management of these cases was made a great deal more difficult by the previous administration of 5-fluorouracil.

All the patients in the series were available for at least a 6 month follow-up. Of the 41 patients treated definitively and available for 6 months follow-up, 38 were alive for a survival rate of 93 per cent. Thirty-nine patients have been followed for 12 months; of these 22 were alive yielding a 12 month survival figure of 56 per cent. There were 35 patients available for a 24 month follow-up of which 17 were living for a survival figure of 46 per cent. There were 32 patients available for a 36 month follow-up, 10 of whom were alive for a survival figure of 31 per cent. There were 29 patients available for a 5 year follow-up, 6 of whom were alive for a survival figure of 21 per cent. (Table 1). These survival figures compare

TABLE I

CARCINOMA OF THE BLADDER—SUMMARY OF RESULTS FROM SUPERVOLTAGE THERAPY FOR PATIENTS TREATED DEFINITIVELY

Group	No. of Cases	Survivals				
		6 Mo.	1 Yr.	2 Yr.	3 Yr.	5 Yr.
1 (Stage 0, A, B1)	4	4/4	4/4	4/4	4/4	4/4
2 (Stage B2, C)	18	16/18	13/17	9/14	5/11	2/9
3 (Stage D)	19	18/19	5/18	3/17	1/17	0/16
All Cases	41	38/41	22/39	17/35	10/32	6/29

quite satisfactorily with those presented by Buschke *et al.*,[3] Fletcher,[4] Friedman,[5] Morrison[9] and Rubin and Buran.[10]

COMPLICATIONS

In evaluating the results from supervoltage radiation therapy, one must consider the complications that occur as a consequence of the therapy. Complications were classified as mild, moderate and major. In defining the mild complications, all cases of cystitis, dysuria and proctitis, which did not persist 6 weeks beyond the completion of radiation therapy, were included. Of the 49 patients treated, all exhibited to a certain degree symptoms that would be classified as mild.

In defining the moderate complications, all cases with persistent cystitis which extended longer than 6 weeks following the completion of treatment, persistent proctitis which extended 6 weeks beyond the completion of treatment, and bladder telangiectasia without severe bleeding were included. There were 6 patients who had moderate complications due to the radiation therapy. Four of these 6 had had previous major pelvic surgery. One had a major transurethral resection, 2 suprapubic cystotomies, and one an abdominal perineal resection.

Major complications were defined as persistent rectal or bladder bleeding, a contracted bladder, ulcerations of the bladder or rectum, fistula formation or death due to complications of radiation therapy. Of the treated group 3 patients exhibited major complications. One had an ulceration of the bladder wall and 2 had fistulae that developed between the bladder and the abdominal wall. In the latter instance, each patient had a previous complicating modality of therapy. One had a previous suprapubic cystotomy and the other several previous courses of conventional radiation therapy.

COMMENT

The administration of 5-fluorouracil immediately prior to the institution of radiation therapy significantly influenced the course of treatment in an undesirable manner. Our ultimate conclusion was that a systemic chemotherapeutic agent should be reserved for those instances in which either surgery or irradiation had failed or where there was systemic manifestation of the disease process.

In spite of definitive supervoltage radiation therapy, 6 patients with Group 2 lesions required a total cystectomy because of persistent disease within the bladder. In each there had been an objective response, as manifested by reduction of tumor mass, to the point where cystoscopy was adequate, having been inadequate prior to radiation therapy. Cystectomy became necessary because of failure of resolution of the tumor in 4 cases and in each instance was performed without difficulty. Cystectomy was planned to follow radiation therapy in 2 cases. The operation was undertaken in an interval that varied from 6 weeks to 3 months following the completion of the radiation therapy. All 6 patients are living and without residual malignancy at 3, 3, 4, 17, 17 and 20 months following the cystectomy.

It would appear, judging from the results of the group treated with combined supervoltage radiation therapy and surgery, that this approach to the problem of carcinoma of the bladder might be considered a possible worthwhile procedure in patients with advanced carcinoma of the bladder without distant metastases. The patient for such consideration should be in good general condition with no medical contraindications to surgery.

CONCLUSIONS

1. Patients with carcinoma of the urinary bladder in whom the lesion extends to the lateral pelvic wall and who are in poor general condition are probably poor candidates for definitive radiation therapy and perhaps are best handled in a palliative manner.

2. Previous courses of orthovoltage radiation therapy limit to a great degree the use of supervoltage radiation therapy in subse-

quent treatment of carcinoma of the bladder.

3. Previous suprapubic bladder surgery is associated with a greater incidence of complications.

4. Chemotherapy utilizing 5-fluorouracil immediately prior to radiation therapy comlpicates the patient's course.

5. Bladder surgery for persistence or recurrence can be performed following supervoltage radiation therapy without significant difficulty.

6. Definitive supervoltage radiation therapy is of value in the management of high grade, deeply invasive lesions. These are lesions that respond poorly to total cystectomy.

7. Whether used alone, or in combination with radical surgery, supervoltage radiation therapy does offer an advantage in the management of urinary bladder tumors.

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HEMANGIOENDOTHELIAL CELL SARCOMA AND HEMANGIOPERICYTOMA*

REPORT OF 9 CASES

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HEMANGIOENDOTHELIAL cell sarcomas and hemangiopericytomas constitute a group of rare neoplasms which present difficult problems in both histologic diagnosis and in clinical management. Although numerous cases are cited in the literature, relatively few have been reported with sufficient information for evaluation of the effect of administered radiation therapy.

Compared with the incidence of benign tumors of blood vessels, the number of malignant tumors is extremely small. Over a ten year period 1,056 benign angiomas and only 20 angiosarcomas were seen at the Memorial Hospital in New York.[8] Four cases of hemangioendothelioma were seen in the Department of Radiation Therapy at Bellevue Hospital and 4 additional cases were seen on other services between 1925 and 1946.[2] Since 1942 a total of 307 cases of hemangiopericytoma has been accumulated from various sources at Columbia University by Kauffman and Stout.[5]

The true incidence of these tumors is obscured by the difficulty in making the histopathologic diagnosis. Five cases of hemangioendothelial cell sarcoma and 4 cases of hemangiopericytoma were treated in the Radiation Therapy Center of The University of Michigan Medical Center between 1932 and 1960. Histopathologic and therapeutic aspects of these cases are summarized in this presentation.

PATHOLOGIC FINDINGS

The hemangioendothelial cell sarcoma and hemangiopericytoma are neoplasms derived from the normal constituents of the capillary. The capillary wall is formed by a continuous layer of endothelial cells surrounded by a sheath of reticular fibers. Contractile cells, the so-called pericytes of Zimmermann, lie outside of this sheath and probably exercise a mild regulatory effect on capillary blood flow.

The hemangioendothelial cell sarcoma is a malignant neoplasm derived from the vascular endothelium.[13] The tumor may be grossly hemorrhagic or relatively avascular. Microscopically, the neoplastic cells may define prominent vascular lacunae or slits; however, in some tumors the overgrowth of cells obscures the vascular markings. Nuclear pleomorphism and increased mitotic activity are usually evident. The neoplastic cells are spindled but in some instances may assume an epithelioid character. Silver impregnation delineates the reticular sheaths and may make the vascular character of the neoplasm more apparent. By this technique a labyrinthine network of anastomosing vascular channels is seen, and the neoplastic cells are present within the sheath. This malignant neoplasm is to be distinguished from the hypertrophic capillary hemangioma, or so-called benign hemangioendothelioma, often seen in early childhood. The latter tumor is quite cellular, but represents a proliferation of capillaries rather than an uncontrolled overgrowth of endothelial cells. Therefore, one sees only a single layer of cells within the reticular sheath. Several neoplasms of children reviewed for this series, which were originally diagnosed as hemangioendothelial

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cell sarcoma but followed a benign course, were found to be hypertrophic capillary hemangiomas.

In 1942 Stout and Murray[16] separated the hemangiopericytoma from other vascular neoplasms; they described the neoplasm as being composed of capillaries surrounded by an accumulation of spindled or oval cells which they felt represented pericytes of Zimmermann. This neoplasm lacks the circumscription, organoid structure, or rich neural component of the glomus tumor, although the histogenesis is similar. Silver impregnation reveals that the proliferating cells lie outside of the reticular sheath. Grossly, these tumors are usually tan or gray and firm. Pleomorphism and increased mitotic activity are not prominent microscopic features. Several authors have cited the lack of correlation between histologic findings and clinical behavior.[5,9,14,15]

CLINICAL FEATURES

The reported series have failed to show a predilection of these tumors for either sex or age. They may occur anywhere capillaries are found and therefore are ubiquitous.

The behavior of both hemangioendothelial cell sarcomas and hemangiopericytomas is variable. In some cases the tumor may remain localized and follow a benign course, while in others the disease is rapidly fatal. A high incidence of metastases has been reported in patients with hemangiopericytomas.[3] Although low survival rates have been recorded in collected cases of hemangioendothelial cell sarcoma,[8,13] long term survivals have also been described.[12,14,16] Both of these tumors metastasize by hematogenous routes, with infrequent lymph node involvement. It has been noted that hemangiopericytomas arising in the lower extremities are particularly prone to metastasize.[5,6,15] A lower grade of malignancy has been reported in one series of hemangiosarcomas of the nasal fossae and paranasal sinuses.[8]

The symptoms depend upon the site of origin of the tumor. Both tumors often exhibit a painless, nontender swelling. The hemangioendothelial cell sarcoma frequently appears vascular, although in some tumors the neoplastic cells may obliterate the vascular channels. Hemangiopericytomas are usually solid, gray, or tan neoplasms. Those tumors occurring in the nasal fossae and paranasal sinuses may produce obstruction of the nasal passages or ostia of the sinuses, epistaxis, and headache. Invasion of bone may produce osteolytic defects. In the absence of invasion, pressure of the tumor may cause erosion of adjacent bone. The roentgenographic appearance of lung metastases does not differ from that seen in other sarcomas. Calcification has rarely been demonstrated roentgenographically within the soft tissue mass.

TREATMENT

It is generally agreed in regard to both hemangioendothelial cell sarcomas and hemangiopericytomas that surgical excision is the best form of treatment.[5,6,10,15] Radiation therapy is utilized when surgical removal is incomplete, when operative treatment would involve an excessively mutilating procedure, or when the neoplasm is inoperable and palliation is desired.[4] In view of the high incidence of recurrence, the use of postoperative irradiation in all cases recently has been advocated.[11]

The response of malignant tumors of the blood vessels to radiation therapy is difficult to evaluate. The published series, of necessity, contain few cases. Often information as to the dose of radiation delivered has been incomplete and the follow-up period short.

In a recent article Friedman and Egan,[4] reporting 5 new cases of hemangiopericytoma and 3 from the literature, evaluate radiation dose in relation to the response of the tumor. These cases apparently represent the only ones in the literature for which a radiation dose is available. One patient with a tumor of the dorsum of the foot showed no recurrence two and one-half years after a tumor dose of 9,288 rads in 70

days, following partial excision. However, metastatic lesions did occur in other locations. The same patient developed a lesion in the left tibia which was treated with a tumor dose of 8,240 rads in 30 days. One year later there was symptomatic cure with roentgenographic evidence of sclerosis in the region of the tumor. The authors concluded that the lethal dose is in the order of 7,500 to 9,000 rads in 30 to 60 days, and the palliative dose a minimum of 3,000 rads in 18 days.

One of the 4 cases of hemangiopericytoma reported by Mujahed, Vasilas and Evans[11] had a pulmonary metastasis which was treated with a tumor dose of 7,100 r in 58 days. At the completion of therapy the mass had shrunk to about one-half of its original size. A second case, presenting as a mass in the right arm, received 4,930 r tumor dose in 24 days. The tumor recurred one year later, and, after excision, a 4,550 r tumor dose was given. This patient expired less than two years after her original admission with massive pulmonary metastases.

Kent[6] reported 1 hemangiopericytoma arising in a leg and reviewed 6 other cases previously reported in the literature. His case was treated with 4,440 r tumor dose in 23 days, and although softening was noted, no regression in size occurred. When bilateral pulmonary metastases appeared, only the left lung was irradiated and after a 2,163 r tumor dose the nodules could no longer be identified. At necropsy only small nodules were found in the left lung in contrast to the right. The 10 cm. primary tumor in the right leg was mostly necrotic but did contain viable neoplasm. Six of the 7 cases in this report received some benefit from radiation therapy.

Four cases of "hemangioendothelioma" of the thyroid gland treated with roentgen rays were reported by Baumann-Schenker[1] in 1935. The neoplasm in 2 of these cases had not recurred or metastasized after two and one-half years and five months, respectively. They received an air dose of 5,000 r to 6,000 r. A case of "hemangioendothelioma" of the face, reported by Drucker,[2] was free of recurrence one and one-half years following treatment with 2,000 r. However, it was stated that the tumor was completely excised before radiation therapy and there was evidently no evidence of persistent neoplasm at the time of irradiation.

Morgenstern, Olivetti, and Westing[10] treated a hemangioendothelial cell sarcoma of the left scapula and clavicle with 2,500 r to the anterior acromioclavicular region and the posterior scapular region in 4 weeks (250 kv.); no recurrence was present five years later. Rubin and Dann[12] reported treatment of an inoperable hemangioendothelioma of the pelvis with a tumor dose of 4,610 r over $3\frac{1}{2}$ months (200 kv.). There was a local recurrence after eleven years when 1,148 r tumor dose was administered. This patient died three years later with metastases to diaphragm and mesenteric lymph nodes.

Review of 7 cases of malignant blood vessel tumors by McCarthy and Pack[8] led to the conclusion that both primary and metastatic lesions were moderately radiosensitive. Radiation did not appear to prolong life but was valuable in palliation. A tumor dose of 3,000 r has been recommended when complete surgical extirpation is in doubt.[7] However, one series of hemangiopericytomas recently reported proved to be "unexpectedly radioresistant."[3] Other authors have also concluded that hemangiopericytomas are radioresistant.[5]

REPORT OF CASES

Case 1. (UMH 381507). A thirty-nine year old female with neurofibromatosis was admitted to The University of Michigan Medical Center in May, 1936, with a large ulcerating neoplasm of the left gluteal region. It had been present for several years but had increased rapidly in size during the six months prior to admission. A chest roentgenogram revealed a rounded mass in the lateral portion of the right upper lung. An excision of the gluteal tumor was attempted; however, due to infiltration of the gluteus maximus, complete excision was impossible. In June, 1936, she received postoperative radia-

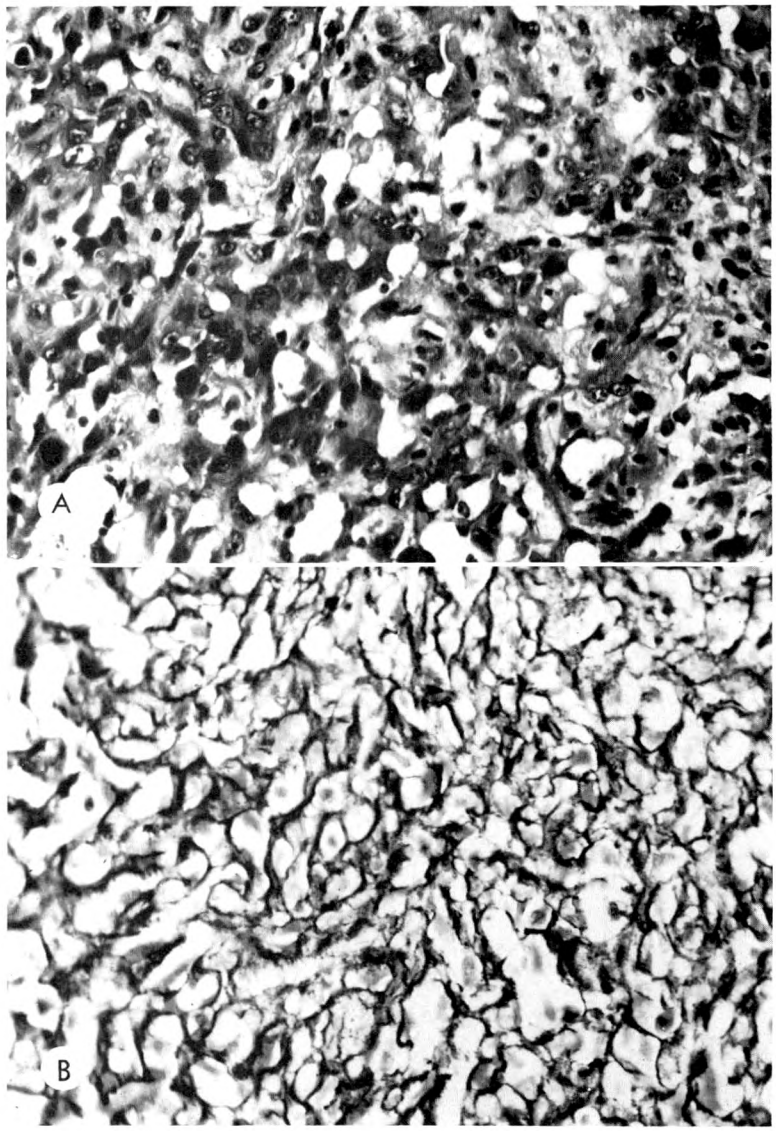


FIG. 1. Case I. Hemangioendothelial cell sarcoma. (*A*) Nuclear pleomorphism and increased mitotic activity are present. Hematoxylin and eosin, ×250. (*B*) The proliferating cells lie within the reticular sheath. Wilder's reticulum stain, ×250.

tion (3,400 r in air in 19 days). In September, 1936, a positive biopsy was obtained from the base of the wound. Chest roentgenograms showed numerous metastases in the lungs. No further treatment was attempted. The patient died on December 14, 1936. Pathologic diagnosis: Hemangioendothelial cell sarcoma (Path. no. 6908-AN) (Fig. 1, *A* and *B*).

CASE II. (UMH 512680). This twenty-one year old white male was first seen at The University of Michigan Medical Center in September, 1942, because of pain in the left chest of four months' duration. Chest roentgenograms showed a 6×7 cm. well-defined posterior mediastinal mass. Because of the possibility that the tumor might be a lymphoma, a test dose of radiation was given (400 r in air to each of 4 chest fields in 4 days). In October, 1942, chest roentgenograms showed a decrease in the size of the mass; however, it was insufficient to warrant a diagnosis of lymphoma. Thoracotomy was done in November, 1942, and a large vascular neoplasm infiltrating adjacent mediastinal

structures was found. Postoperative radiation was given (3,000 r in air, anterior and posterior fields, in 26 days). In November, 1943, he developed hoarseness and weight loss was noted. There was a complete paralysis of the left vocal cord and the chest roentgenogram showed a recurrent mass at the site of the original tumor. No further treatment was given. The patient died in March, 1944, but there was no necropsy. Pathologic diagnosis: Hemangioendothelial cell sarcoma (Path. no. 2521-AU).

Case III. (UMH 737794). This sixty year old white female was admitted to The University of Michigan Medical Center in February, 1955. She gave a history of a painful mass in the right inguinal region of one year's duration. On physical examination a firm, 7 cm. mass was found in the region of the fossa ovalis. This appeared to extend upward under the inguinal ligament continuous with a 5×10 cm. mass in the right iliac fossa. The patient's white blood cell count was 21,000 and a diagnosis of chronic lymphocytic leukemia was made. The mass was unresectable but it was biopsied and the patient was referred for radiation therapy (2,500 r in air, anterior and posterior pelvic ports, in 29 days; 2,600 r in air, upper thigh, in 18 days). Two and one-half months after completing therapy, the patient felt much better. Pain in the right femoral region disappeared and the tumor decreased markedly in size. No change occurred for about a year when the tumor began to increase in size. Another course of irradiation was administered (4,125 r maximum to right lower abdomen and right inguinal region in 30 days using Co^{60}). Two months later some decrease in pain and in the size of the mass was noted. Seven months later there was marked enlargement of the tumor in the iliac fossa (17×12 cm.) and 2 nodules had appeared in the left thigh. A chest roentgenogram demonstrated multiple nodules in the lungs. The patient was hospitalized elsewhere and pursued a progressively downhill course despite nitrogen mustard therapy. Death occurred in December, 1957. Pathologic diagnosis: Hemangioendothelial cell sarcoma (Path. no. 7003-BG).

Case IV. (UMH 350856). This twenty-two year old female was referred to The University of Michigan Medical Center in December, 1934, by her physician after he had performed a celiotomy and found a large vascular retroperitoneal pelvic mass. On physical examination pain on motion and edema of the right leg, and a firm nodular mass filling the entire right side of the pelvis were noted. The possibility that this might represent lymphosarcoma was considered and a test of radiation was given (600 r in air, to each of four 15×20 cm. pelvic ports, in 4 days). There was slight decrease in the size of the tumor and in the edema of the right leg immediately following cessation of treatment. The patient died in uremia one month later and a necropsy was performed. A large, partially necrotic and hemorrhagic tumor was present in the pelvis, protruding posteriorly through the sciatic notch. It appeared to arise in the gluteal muscles. There was bilateral chronic purulent pyelonephritis. No metastases were found. Pathologic diagnosis: Hemangioendothelial cell sarcoma (Path. no A-264-AM).

Case V. (UMH 922083). This sixteen year old white male was first seen in March of 1959 with a history of low back pain, difficulty in walking, and cramps in the legs for a period of three months. Roentgenograms of the lumbar spine showed a lytic lesion in L5. There was myelographic evidence of an extradural defect with complete block at L4. A laminectomy at the L4 and 5 level disclosed a well-encapsulated, extremely vascular, friable neoplasm in an anterior extradural location, displacing the cauda equina posteriorly. Only subtotal removal could be accomplished. Postoperative irradiation was given (4,000 r maximum to a 12×10 cm. lumbosacral field in 23 days using Cs^{137}). He was readmitted in March, 1960, at which time a 4×5 cm. soft mass was palpated in the left lower quadrant of the abdomen. A chest roentgenogram showed metastases in the lungs (Fig. 2). In May, 1960, he was given 0.4 mg./kg. of nitrogen mustard, followed by several courses of triethylene malamine with minimal effect. Further increase in size of the abdominal mass, progression of the neurologic deficit, and development of skull metastases occurred. He died in November, 1960, with widespread metastases. Necropsy was not performed. Pathologic diagnosis: Hemangioendothelial cell sarcoma (Path. no. 7742-BK).

Case VI. (UMH 934030). This sixteen year old male was referred to The University of Michigan Medical Center in September, 1959, with a seven year history of low back pain. Two weeks prior to admission he developed obstipation and anorexia, accompanied by a 10 pound

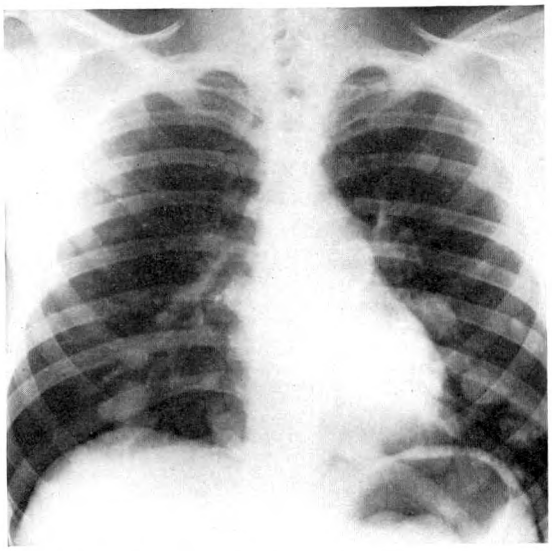


FIG. 2. Case v. Hemangioendothelial cell sarcoma. May, 1960: Bilateral pulmonary metastases.

weight loss. At operation a 10×12×8 cm. firm mass was found in the presacral area. It displaced the rectum anteriorly, and was firmly fixed to the sacrum. Total resection was not possible. Postoperative radiation therapy was given (4,176 r tumor dose in 29 days using Co^{60}). A chest roentgenogram on March 8, 1960, demonstrated 2 pulmonary nodules in the left lower lobe, 3×6 cm. in size, and a compression deformity of D5 (Fig. 3*A*). The patient was given 28 mg. of nitrogen mustard. Subsequent roentgenographic examination of the chest showed almost complete disappearance of 1 pulmonary nodule and a decrease in the size of the other (Fig. 3*B*). When last seen in March, 1961, the liver edge was palpable 8 cm. below the costal margin and there was a 7×7 cm. mass on its anterior surface. No presacral mass could be detected. The lung nodules remained unchanged. Pathologic diagnosis: Hemangiopericytoma (Path. no. 1922-BL).

CASE VII. (UMH 693300). This sixteen year old Negro girl was admitted in November, 1950, with a history of a lump on the right side of the neck which first appeared in October, 1949, and progressively enlarged. A tender mass, the size of a small orange, was present in the right side of the neck under the angle of the mandible. A biopsy was reported as spindle cell sarcoma and a subsequent radical resection with right radical neck dissection was performed. The lymph nodes were negative. Local recurrence of the mass led to re-admission in March, 1951. Chest roentgenograms showed bilateral pulmonary nodules. Palliative radiation therapy to the neck mass was given in April, 1951 (200 kv., 2,500 r in air to opposing 9×7 cm. cervical fields). No decrease in the size of the mass was observed. In May, 1951, following a normal term pregnancy, the patient delivered a viable infant. By September, 1951, 3 large ulcerated masses had

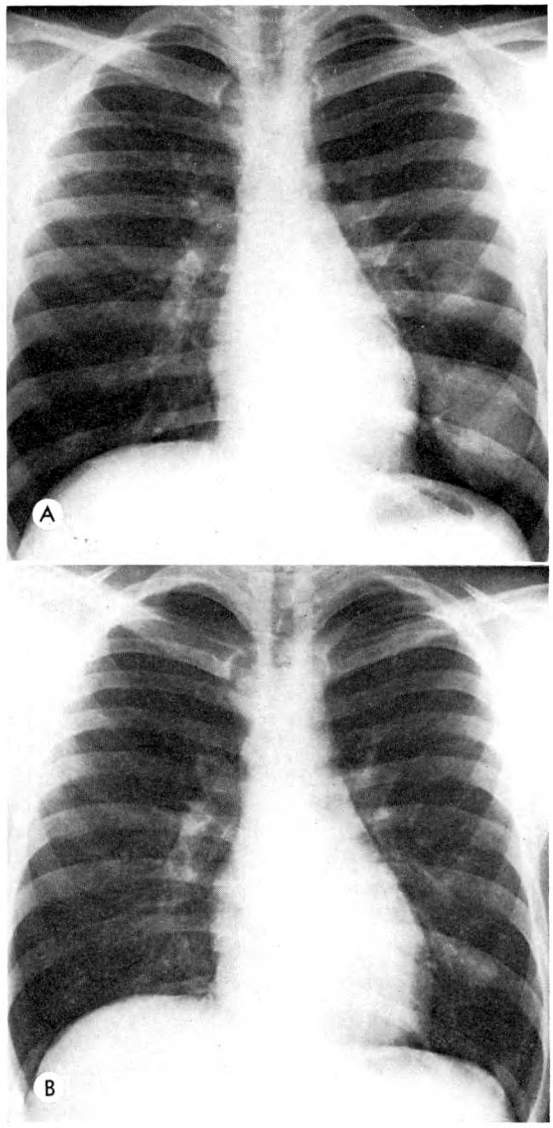


FIG. 3. Case VI. Hemangiopericytoma. (*A*) March, 1960: Pulmonary metastases of left lower lobe. (*B*) August, 1960: Marked decrease in the size of the pulmonary lesions following nitrogen mustard therapy.

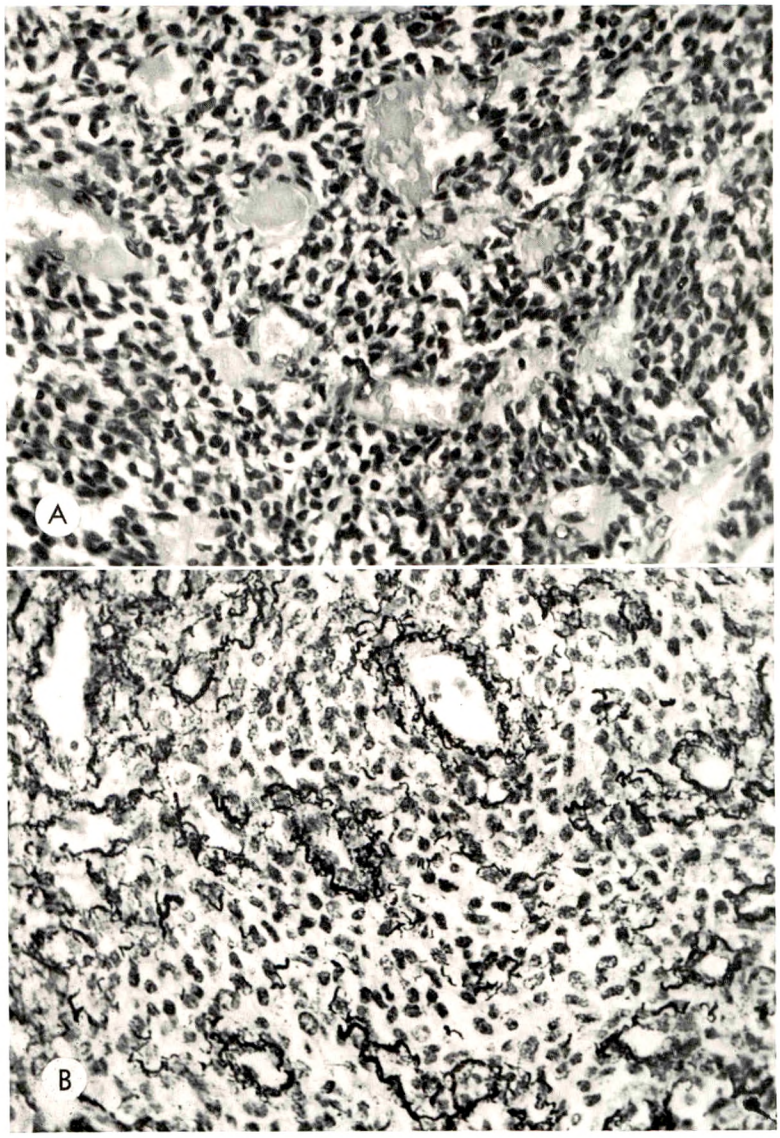


Fig. 4. Case VIII. Hemangiopericytoma. (*A*) Neoplastic cells are relatively uniform in size and staining properties. Hematoxylin and eosin, ×185. (*B*) The cells lie outside of the vascular reticular sheath. Irregular reticular fibers are adjacent to many of the cells. Wilder's reticulum stain, ×185.

developed in the neck. The patient had right hemiplegia. She died on October 3, 1951. Necropsy was not performed. Pathologic diagnosis: Hemangiopericytoma (Path. no. 3235-BC).

Case VIII. (UMH 243769). This forty year old man was first seen at The University of Michigan Medical Center on July 3, 1930. He was found to have a soft polypoid tumor in the left nasal fossa. The tumor was removed in June, 1931. A local recurrence of the tumor was found in September, 1934. Operation was advised but the patient did not submit to this until May, 1936. At that time left external ethmoidectomy and left Caldwell-Luc procedures were performed. In June, 1936, there was evidence of recurrence in the region of the posterior ethmoid sinuses. Radiation therapy was administered (2,400 r in air to a 10×8 cm. field in 19 days). The patient was next seen in October, 1953, at which time the entire nasopharynx was filled with polypoid masses containing areas of necrosis. He did not return for treatment. In

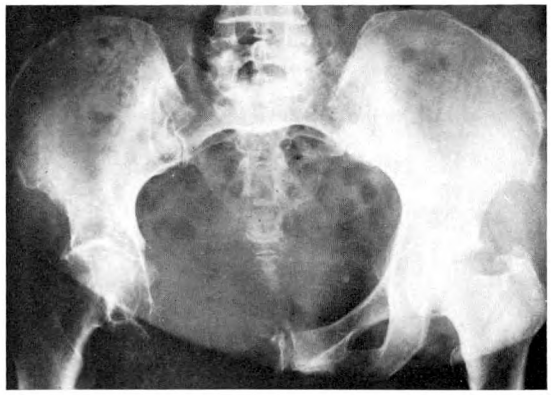


FIG. 5. Case IX. Hemangiopericytoma. May, 1959: Soft tissue mass in the right side of the pelvis with destruction of the right ischium and pubis.

August, 1956, this patient received radiation therapy for a recurrence of the nasal tumor at another hospital. No additional follow-up is available. Pathologic diagnosis: Hemangiopericytoma (Path. no. 7274-AN) (Fig. 4, *A* and *B*).

CASE IX. (UMH 859956). This forty-eight year old woman was admitted to The University of Michigan Medical Center in January, 1957, with a tumor of the right upper thigh. On physical examination a hard fixed mass, 15×12×8 cm., was found in the adductor region of the right thigh; it extended into the right side of the pelvis and encroached on the vagina and rectum. Roentgenograms of the pelvis showed destruction of the right ischium and pubis (Fig. 5). The mass was thought to be inoperable and radiation therapy was administered (11×11 cm. pelvic fields, dose at 12 cm. 3,012 r using Co^{60}; right anterior thigh 4,175 r maximum in 38 days). Some symptomatic relief was obtained, but there was little change in the size of the mass. November, 1958, roentgenograms showed increased destruction of the pelvic bones. The mass had enlarged and filled the major portion of the right side of the pelvis and femoral area. In October, 1959, perfusion of the pelvis with nitrogen mustard was done, followed by considerable symptomatic relief. In March, 1960, it was necessary to perform bilateral dorsal cordotomy for relief of pain. Metastatic nodules were present in the lungs. She died in May, 1960, but permission for necropsy was not obtained. Pathologic diagnosis: Hemangiopericytoma (Path. no. 3430-LBI).

RESULTS

Seven of the 9 patients reported above died with neoplasm. Five had extensive disseminated neoplasm at the time of death. One died of local extension of neoplasm which obstructed the ureters. No metastases were found at necropsy (Case IV). Another patient, Case II, evidently died with local extension of the neoplasm, but no record is available relative to the presence or absence of metastases. One of the 2 living patients has disseminated disease, while the other experienced numerous recurrences but no distant metastases over a twenty-five year period.

In the 6 cases with disseminated disease, the chest roentgenograms revealed pulmonary metastases. Other sites in which metastases were apparent before death were skull, central nervous system, and liver. The single patient upon whom a necropsy was performed showed no evidence of metastases. No involved lymph nodes were found in the radical neck dissection specimen in Case VII.

The cases of neoplasms arising in the gluteal region had the shortest survival times. The patient with the nasal fossa tumor was the only one who showed multiple local recurrences. Survival times based on the date that the patient first received treatment are given in Table I.

Six patients in this group were treated by resection followed by radiation therapy. Four of these cases had no perceptible tumor at the primary site at the time of radiation, but it was the impression of the surgeon that resection was subtotal. All of these showed evidence of local recurrence after irradiation except I (Case VI), and that patient is alive with disseminated neoplasm one year following irradiation of the primary site. A recurrence at the primary site was irradiated with no effect in Case VII. Only in Case VIII did the tumor appear markedly radiosensitive, and long periods of regression followed the radiation therapy.

Three patients received radiation to the

TABLE I

SURVIVAL TIME

	Primary Site	Metastases	Follow-up	Dead
		Hemangioendothelial Cell Sarcoma		
Case I	Gluteal region	Disseminated	7 mo.	Yes*
Case II	Posterior mediastinum	No record	1 yr., 5 mo.	Yes*
Case III	Inguinal region	Disseminated	2 yr., 8 mo.	Yes*
Case IV	Gluteal region	None	2 mo.	Yes*
Case V	Extradural L_{4-5}	Disseminated	1 yr., 7 mo.	Yes*
		Hemangiopericytoma		
Case VI	Presacral	Disseminated	1 yr., 6 mo.	No*
Case VII	Submaxillary area	Disseminated	1 yr.	Yes*
Case VIII	Nasal fossa	None	25 yr.	No*
Case IX	Upper thigh	Disseminated	3 yr., 4 mo.	Yes*

* With neoplasm.

primary site without prior operative procedure. One of these had fairly good palliation lasting more than a year after the first course of therapy, and several months after the second. Case IV received such a small dose of radiation that it was not considered to be a worthwhile attempt at palliation. Case IX obtained minimal palliative effect after supervoltage irradiation.

The details of the technique of radiation therapy in each case are given in Table II. Four patients were treated with supervoltage irradiation. Several of the cases were treated many years ago with orthovoltage modalities. In 2 cases (Cases VI and IX) a tumor dose had been determined. A tumor dose of 3,012 r in 38 days in Case IX had minimal effect. In Case VI a tumor dose

TABLE II

TECHNIQUE OF RADIATION THERAPY

Case No.	kv.	HVL	FSD	Field Size	r	Days	Response
				Hemangioendothelial Cell Sarcoma			
I	200	.9 Cu	50 cm.	15×20 cm.	3,400 air	19	Minimal
II	200	.9 Cu	50 cm.	12×14 (4)*	400 air	4	Minimal
2nd course	200	.9 Cu	50 cm.	15×15 (2)†	3,000 air	26	Unknown
III	220	1.2 Cu	50 cm.	14×12 (2)†	2,500 air	29	Good
				10×9	2,600 air	18	Good
2nd course	Co^{60}		73.3 cm.	11×11	4,125 max.‡	30	Slight
				11×11	4,125 max‡	30	Slight
IV	200	.9 Cu	50 cm.	15×20 (4)*	600 air	4	Minimal
V	Cs^{137}		50 cm.	12×10	4,000 max.‡	23	Unknown
				Hemangiopericytoma			
VI	Co^{60}		73.3 cm.	11×11 (2)†	4,000 TD§	23	Unknown
VII	200	1.0 Cu	50 cm.	9×7 (2)†	2,300 air	18	None
VIII	200	1.0 Cu	50 cm.	10×8	2,400 skin	19	Good
IX	Co^{60}		73.3 cm.	11×11 (2)†	3,012 TD§	38	Minimal
				11×11	4,175 max.‡	30	Minimal

* (4) Indicates 2 anterior and 2 posterior pelvic fields; dose is that delivered to each.
† (2) Indicates opposing fields.
‡ Maximum dose.
§ Tumor dose.

of 4,176 r in 29 days was delivered followed by nitrogen mustard therapy. No local recurrence has developed.

Four patients received one or more courses of nitrogen mustard. Two of these showed no significant palliation. Case V also received TEM with no definite effect. Case VI had a good response to nitrogen mustard with a marked decrease in the size of pulmonary nodules five months later. No new pulmonary lesions developed and growth of those previously present has not yet occurred. A new mass developed in the liver about one year after the nitrogen mustard was administered. Case IX had perfusion of the pelvis with nitrogen mustard with considerable symptomatic relief.

DISCUSSION

In general, the results obtained by radiation therapy in this group of cases have been poor. Since radiation therapy failed to eradicate any of these neoplasms, the lethal dose must be high. This was also the conclusion of Friedman and Egan.[5] To deliver a dose of this magnitude carries such great danger of complications as to be unfeasible. Likewise, there is insufficient evidence that such a dose would be tumoricidal. It is possible that palliation might have been obtained in some cases if somewhat higher doses had been used.

The great difficulty often experienced by the pathologist in arriving at the histologic diagnosis must be kept in mind when evaluating these tumors. In a group of 32 cases treated as malignant blood vessel tumors at the Radiation Therapy Center of The University of Michigan Medical Center since 1932, reappraisal of the histologic material led to reclassification of all but these 9 reported cases. Cases in which the final diagnosis was in doubt were omitted. As reported by others,[9] attempts to correlate the histologic features of hemangiopericytoma with the response to radiation or with the clinical course were largely unsuccessful. Correlation of the clinical course with the histologic appearance of hemangioendothelial cell sarcoma was somewhat more successful. The high degree of malignancy of the tumors arising in the lower extremities and pelvis and the diminished tendency of tumors of the nasal fossa to metastasize, as previously reported,[6,8,18] were confirmed in this series.

SUMMARY

1. Five cases of hemangioendothelial cell sarcoma and 4 cases of hemangiopericytoma are reported. Seven of these patients died with neoplasm. One is alive with disseminated disease, while the other patient has experienced numerous recurrences at the primary site.

2. The pathologic diagnosis of these tumors is difficult. It was not possible to correlate definitely the histologic appearance of the hemangiopericytoma with response to radiation or with the clinical course. Similarly, the aggressiveness of hemangioendothelial cell sarcoma could not be uniformly predicted from the histologic findings.

3. Radiation therapy was successful in producing significant palliation in 2 cases. This group of tumors was generally radioresistant. However, occasionally, a definite radiosensitivity was manifest. The value of chemotherapeutic agents in certain cases should not be overlooked. The lethal tumor dose must be very high and it is extremely difficult or impossible to deliver a dose of this magnitude. Consequently, surgical removal is the treatment of choice for both of these neoplasms when the possibility of cure exists.

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TUMOR CALCIFICATION FOLLOWING THERAPY*

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CALCIFICATION in soft tissue is a phenomenon well known to roentgenologists. It is also recognized that calcification in tumors, both benign and malignant, is not unusual. Different types of neoplasms calcify with variable frequency; the roentgenographic demonstration of a heavily calcified uterine fibroid is a familiar experience, while certain other tumors calcify seldom, if ever. Primary tumors commonly undergo this change; metastases rarely do. The deposits vary in site and appearance; the psammomatous type which occurs in the epithelium of tumors arising, for example, in the ovary, can be contrasted with the coarser collections seen in the necrotic areas of degenerating neoplasms such as hypernephromas and brain tumors, the discrete rounded calcifications (phleboliths) of hemangiomas, the ossifications of teratomas, or the stippled calcifications of breast carcinomas. Indeed, the type of calcification roentgenographically demonstrated may on occasion suggest the histopathologic diagnosis.

Calcification in areas of degeneration and necrosis in tumors might be expected to occur with appreciable frequency following effective therapy *in situ* of large tumors, at least. However, no such cases have yet been reported.

At The University of Texas M. D. Anderson Hospital and Tumor Institute, calcification in tumor following therapy has been recognized roentgenographically in 15 instances.

DISCUSSION OF CASES

In Table 1 a brief outline of the findings in the 15 patients comprising this series is given.

All these tumors originated in soft tissue. Deposition of calcium in the soft tissue component of osseous tumors has been observed frequently in this institution following high dosage radiation therapy under anoxic conditions. However, tumors of bone form a separate problem, and are not included in this study.

In no case was calcium demonstrated in the tumor or its metastases, if any, prior to therapy.

Thirteen patients were subjected to irradiation and 2 received chemotherapy.

The time factors given in the chart are in some cases estimates. The intervals given reflect the roentgenographic findings accurately, but roentgenograms may not have been obtained at sufficiently short periods following therapy to show the earliest manifestations of calcium deposition. Also, in certain instances, the examinations were too infrequent to show the pattern of development in detail.

Most of the tumors in which calcification appeared are not commonly subject to such change. With all of them the evolution of events implicates as the most probable causative agent the therapy which was administered. In most cases, the tumor was initially fairly massive, and 10 of the 15 cases demonstrated marked shrinkage, either clinically or roentgenographically, during the appearance of calcium deposits. As far as one can tell from those cases in which roentgenograms were obtained at a sufficiently short interval following therapy and with adequate frequency subsequently, the calcific changes appear at or prior to the mass reaching minimum size. The decrease in the size of the neoplasm did not always parallel the clinical course of the patient, though the calcified area seemed to take a less active part in the subsequent progression of the disease process. Particularly in the 2 cases undergoing chemo-

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TABLE I

TUMOR CALCIFICATION FOLLOWING THERAPY: 15 CASES FROM THE M. D. ANDERSON HOSPITAL

Case	Age	Color	Sex	Diagnosis	Therapy*	Objective Therapeutic Response	Site of Calcification	Interval: Therapy to Calcification	Interval: Appearance of Calcification to Stability	Type of Calcification	Regrowth of Mass	Present Status of Patient: Interval since Therapy
1. J.G.	14	W	M	Hodgkin's disease (granuloma)	1,500 r total abdomen + 1,000 r right pelvis (6 weeks)	Marked decrease in right pelvic mass	Right pelvic tumor	8 months	31 months	Coarse nodular; small plaques	No	Alive with disease (5½ years)
2. J.W.	11	W	F	Hodgkin's disease (granuloma and paragranuloma)	2,000 r mediastinum + 2,500 r upper abdomen (5 weeks)	Marked decrease in both abdominal and mediastinal masses	Hilar areas Abdominal tumor	20 months (mediastinum) 5 months (abdomen)	16 months 16 months	Coarse nodular; 2 mm. rings	No	Alive with disease (5½ years)
3. R.P.	33	N	M	Hodgkin's disease	2,000 r axilla + 2,000 r supraclavicular (3 weeks)	Mass disappeared	Axillary and supraclavicular areas	Not known	Not known (stable at present)	Coarse nodular	No	Apparent cure (13 years)
4. D.L.	30	W	M	Hodgkin's disease	1,400 r upper abdomen (3 weeks) 1,300 r upper abdomen (3 weeks) (39 months between treatments)	Poor: slight shrinkage at each treatment	Abdominal tumor	23 months	Not stable at 39 months Not stable at 32 months	Coarse nodular; confluent areas; 2 mm. rings	Yes (initial treatment) No (final)	Alive with disease (6 years)
5. J.H.	62	W	M	Lymphocytic lymphosarcoma	1,500 r right kidney (3 weeks)	Marked shrinkage of kidney	Right renal parenchyma	7 weeks	Not stable at death (17 weeks)	Coarse nodular; 2 mm. rings; small spicules	No	Died of disease (6 months)
6. W.J.	39	W	M	Reticulum-cell sarcoma	2,000 r para-aortic (6 weeks) + 750 r total abdomen (2 weeks)	Slight shrinkage of abdominal mass	Retroperitoneal tumor	4 months	Not stable at death (2 months)	Irregular, coarse rings; small spicules	No	Died of disease (6 months)
7. M.M.	4	W	M	Reticulum-cell sarcoma	Cytoxan 3.8 gm. (2 months) Purinethol 3.5 gm. (3 months) Methotrexate 130 mg. (4 months)	Poor: slight decrease in renal size	Left renal area	7 months	Not stable at death (3 months)	Amorphous	Yes	Died of disease (10 months)
8. F.P.	26	W	M	Thyroid carcinoma, papillary and follicular	4,000 r mediastinum + I^{131} 15 mc	Excellent	Mediastinal metastasis	17 months	41 months	Shell like; amorphous plaques	No	Apparent cure (7½ years)
9. B.H.	12	W	M	Thyroid carcinoma, papillary and follicular	I^{131} 200 mc	Excellent	Mediastinum, supraclavicular area, neck	17 months	47 months	Punctate to coarse nodular; small plaques	No	Apparent cure (8½ years)
10. D.W.	35	W	F	Neuroblastoma, recurrence after excision	2,100 r abdomen (4 weeks) + 3,500 r right upper abdomen (6 weeks)	Poor	Retroperitoneal area, including involved lymph nodes	9 months	Not stable at death (8 months)	Fine punctate to coarse granular; small plaques	No	Died of disease (17 months)

* 220 or 250 kv., Thoraeus III filter, 70 cm. target-skin-distance, except where otherwise noted.

(*Continued on next page*)

TABLE I—*Continued*

Case	Age	Color	Sex	Diagnosis	Therapy*	Objective Therapeutic Response	Site of Calcification	Interval: Therapy to Calcification	Interval: Appearance of Calcification to Stability	Type of Calcification	Regrowth of Mass	Present Status of Patient: Interval since Therapy
11. H.H.	60	W	F	Carcinoma of breast; paraspinal metastasis	Roentgen therapy to mass; details unknown	Good: shrinkage and relief of pain	Paraspinal mass	7 months	Not stable	Fine punctate	No	Alive with disease (9 months)
12. L.S.	25	W	F	Carcinoma of cervix III-A	76 hour radium application + 6,000 r total pelvis (betatron)	Good	Right adnexal tumor	16 months	27 months	Coarse granular	No	Alive without apparent disease (3½ years)
13. J.M.	25	W	M	Embryonal carcinoma left testis	Nitrogen mustard 24 mg. (2 doses) + Methotrexate 195 mg. (2 weeks)	Good	Retroperitoneal metastasis	2 months	Not stable (3 months)	Coarse irregular granules; small plaques	No	Alive with progressive disease (5 months)
14. J.G.	7	W	M	Glioblastoma multiforme	3,500 r left frontoparietal area	Nil	Intracranial tumor	9 weeks	Not stable at death (7 weeks)	Punctate; some small plaques	Yes	Died of disease (16 weeks)
15. N.H.	15	W	F	Dysgerminoma right ovary	4,000 r retroperitoneal metastasis (massive) Co^{60} therapy	Excellent	Retroperitoneal mass	5 weeks	Not stable (29 months)	Punctate; 1 cm. areas of confluence	No	Alive without apparent disease (2½ years)

therapy, despite the local response at the site of calcification, the patients declined rapidly.

In none of the cases, as far as was verifiable, did other than local factors play any part. None of the patients had tuberculosis, hyperparathyroidism, serum calcium or phosphorus abnormalities, or any of the other more or less generalized abnormalities which lead to deposition of calcium in soft tissues.

The tumor dose in one patient who was treated elsewhere is uncertain, but otherwise the therapeutic schedules are accurately known.

The location of the calcified mass is somewhat unusual in Cases 2, 4, and 13. In Case 2, the mass was anterior to and fixed to the lower pole of the right kidney (Fig. 1, *B* and *C*). In Case 4, it appeared to develop in relation to the lesser curve of the stomach, presumably in peripancreatic lymph nodes (Fig. 2). The marked enlargement allowed the calcified portion to impinge on the stomach. The metastatic mass in Case 13 developed in a location immediately anterior to the retroperitoneal lymphatic system (Fig. 3 *A*). It probably represented disease which completely replaced the lymph nodes in which it was implanted, and extended more readily anteriorly.

Lymphangiography has become a popular method of investigation at this institution (we have undertaken this procedure in over 200 patients) and 2 of the cases, 4 and 13, underwent this examination. In Case 4, the calcified mass was connected to the lymphatic system by at least one channel, and a small amount of contrast material was deposited in the tumor near its periphery in an irregular fashion (Fig. 2*D*). The metastatic neoplasm in the other case revealed no connection with the retroperitoneal lymphatics, but was in contiguity with them and displaced the lymph nodes and lymph vessels to a minor degree (Fig. 3*B*). The demonstrated lymph nodes were shown to harbor metastatic deposits.

Five patients came to autopsy. In none of these was calcium initially reported by

the pathologist. This is not surprising as special staining procedures and a search for calcification are not usually made. In all 5 of these cases, it was specifically noted in the autopsy report that extensive necrosis was present in the area in which calcium deposition was noted roentgenographically. The specimens have since been reviewed; calcium was demonstrated in all. The deposits were in the form of coarse crystals irregularly deposited in necrotic areas. In Case 10, the calcium was located predominantly in fibrous tissue strands adjacent to large areas of necrosis (Fig. 4).

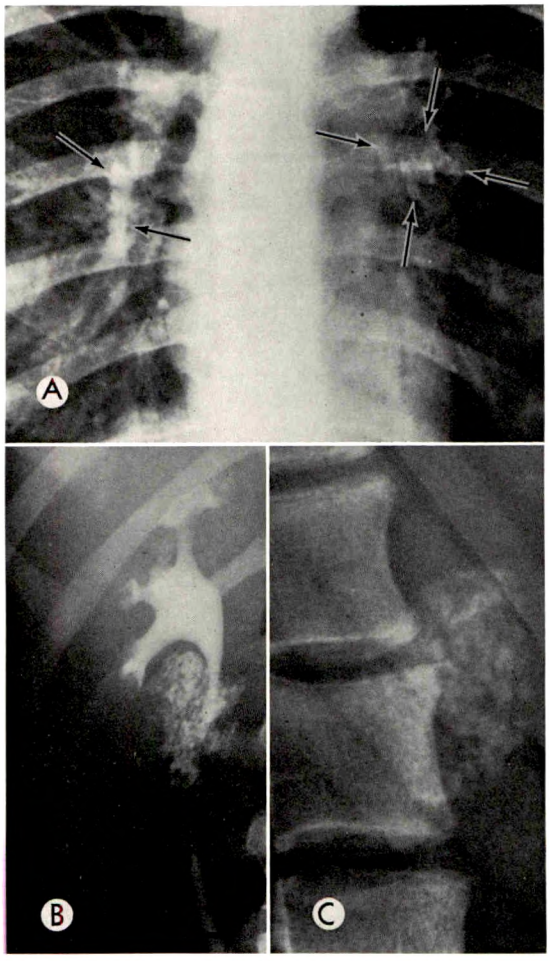


Fig. 1. Case 2. Hodgkin's disease. (*A*) Calcification in hilar regions, 39 months after radiation therapy. This is apparently stable. (*B* and *C*) Calcification in prerenal mass, 21 months after abdominal irradiation. There had been no change over the preceding 5 months.

Despite treatment of multiple areas in several patients, only one patient demonstrated calcium deposition in more than one region. This individual had a lymphoma (Case 2) and demonstrated calcific changes in the pulmonary hili and the abdomen (Fig. 1, *A*, *B* and *C*). In the remaining 14 patients, the site of deposition varied somewhat, though in the majority of cases it was abdominal. The exceptions are 1 case of Hodgkin's disease in which the calcification developed in irradiated axillary and supraclavicular lymph nodes (Fig. 5, *A* and *B*); 2 cases of thyroid carcinoma, in one of which mediastinal and cervical calcification developed following I^{131} therapy (Fig. 6), in the other mediastinal deposits appeared subsequent to I^{131} therapy supplemented by external irradiation; and an infant with a glioblastoma multiforme in which calcification was demonstrated following external irradiation. In 2 cases the calcification developed in an irradiated kidney which was infiltrated by lymphosarcoma (Fig. 7, *A* and *B*).

Excluding the lymphomas, 6 of the tumors were metastatic, unusual sites in which to find calcium deposits.

Case 9 merits further discussion as it demonstrates graphically the relationship between the site of irradiation and the location of the subsequent calcification. This patient was a 12 year old white male who had a total thyroidectomy and right radical neck dissection for thyroid carcinoma, papillary and follicular; carcinoma was present in 14 lymph nodes. Over the next 3 years, the patient had a total of 4 mc of I^{131} administered in doses measuring approximately 150 μc, as attempts were made via the administration of various drugs to increase the pickup from less than 10 per cent to a point where I^{131} therapy would be feasible. Uptake occurred only in the left superior mediastinum, supraclavicular region, and neck. Subsequently, when iodine pickup had increased to a satisfactory level, 200 mc of I^{131} was given as a therapeutic dose. The measurable activity was limited to the same areas as previously

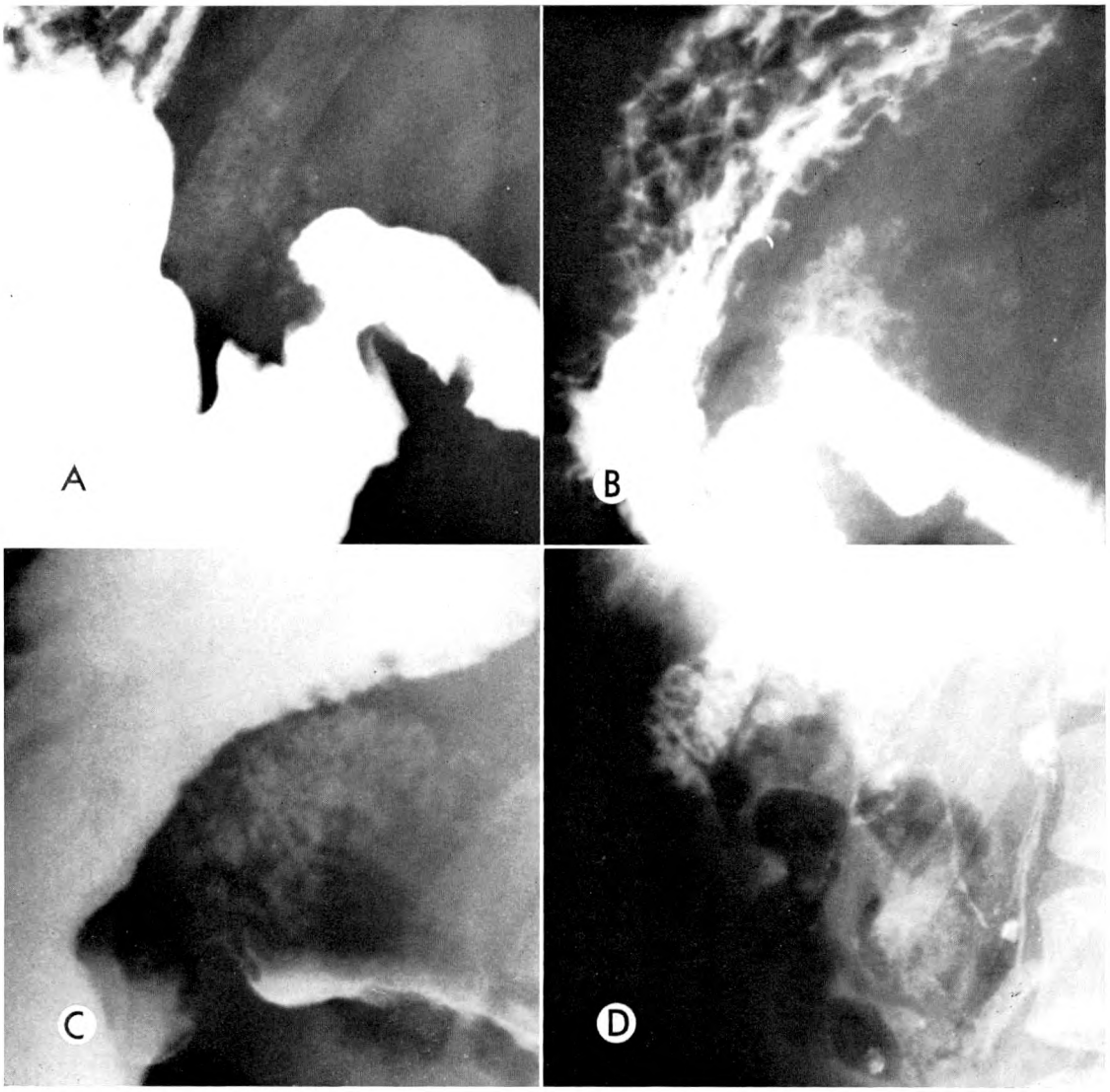


FIG. 2. Case 4. Hodgkin's disease. Calcification in intra-abdominal mass. Initial radiation therapy was administered in February, 1956; a second course was given in May, 1959. (*A*) December 23, 1957. (*B*) April 8, 1959. (*C*) April 26, 1961. (*D*) Lymphangiogram, January 15, 1962. The calcified mass can be seen anteriorly, with an opacified lymphatic channel reaching its posteroinferior aspect and a small, irregular deposit of contrast medium in the noncalcified portion of the tumor.

mapped. At this time, no calcification was present. Following treatment, calcification developed in the left superior mediastinal, supraclavicular, and neck lymph nodes, the distribution of calcification being an almost exact image of the tracings made to map the areas of I^{131} pickup (Fig. 6). These calcifications appeared 17 months after treatment, increased in amount over a 30 month period, and have now been static for the past 21 months.

Case 8 is almost as striking. This patient's mediastinal disease, metastatic from carcinoma of the thyroid, was treated with 4,000 r to the mediastinum over a 5 week period, followed by 15 mc of I^{131}. All of the demonstrable uptake was located in the area in which calcification subsequently developed.

Also noteworthy is the infrequency of the

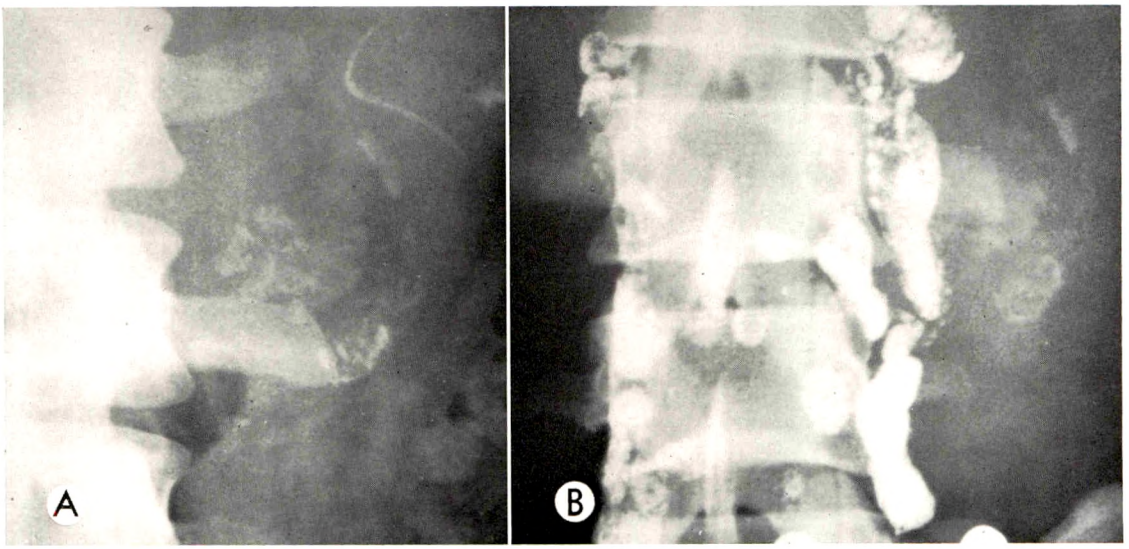


Fig. 3. Case 13. Embryonal carcinoma, left testis, with retroperitoneal metastatis. (*A*) Calcified retroperitoneal metastatic mass deviating the ureter laterally, 3 months post therapy. (*B*) Lymphangiogram. The mass did not opacify but metastases can be seen in the retroperitoneal lymph nodes.

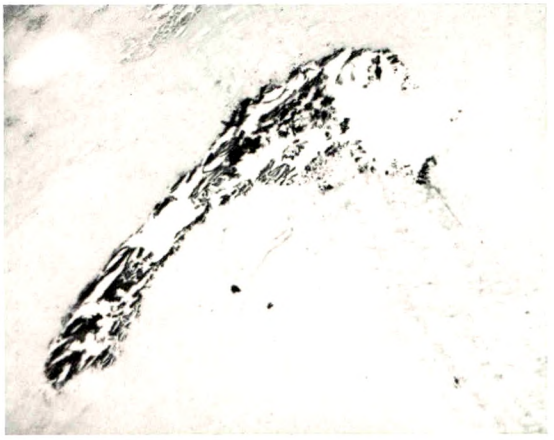


Fig. 4. Case 10. Recurrent neuroblastoma. Dense hyaline matrix with large deposit of crystalline calcium. H&E×80. Calcium was deposited immediately adjacent to areas of necrosis in the recurrent tumor as well as in nearby lymph node metastases.

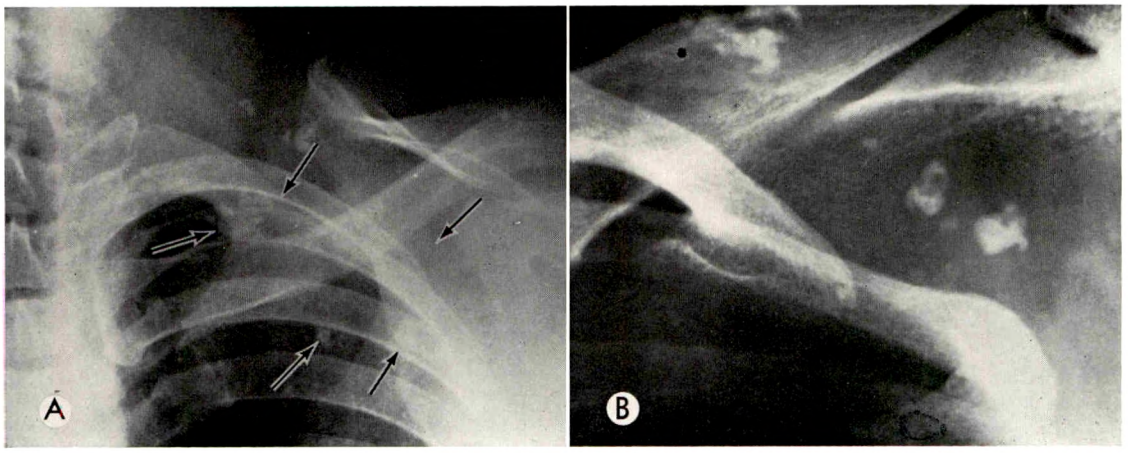


Fig. 5. Case 3. Hodgkin's disease. (*A* and *B*) Calcification in supraclavicular and axillary lymph nodes 10 years after radiation therapy.

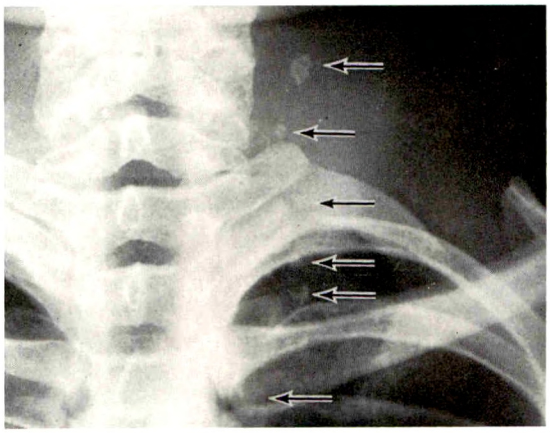


Fig. 6. Case 9. Metastatic carcinoma of thyroid. Calcification in chain of lymph nodes following I^{131} therapy.

appearance of calcification and the different distribution in the mediastinum as compared to the abdomen. Only in Cases 2, 8 and 9 did calcium appear in the mediastinal region, despite the large number of cases in which rather massive mediastinal tumors have been given high doses of radiation therapy. Case 2 exhibited a much more rapid appearance of calcium in the abdominal mass, and a much more complete and rapid distribution of calcium throughout the irradiated prerenal tumor as compared with that appearing in the hili. The individual deposits of calcium do not appear much different in the two sites. The explanation does not appear to lie only in the usually greater volume of tumor tissue involved in the abdomen; calcification has appeared in lymph nodes which were only moderately enlarged at the time of treatment (Case 9), so that size alone is not the determining factor.

The treatment range is too narrow to draw any conclusions regarding its specific effect; external irradiation tumor dosage varied from 1,500 r to 4,000 r without specific dose relationship. The chemotherapeutic schedules are shown in 2 cases (7 and 13) which received no radiation therapy.

The single case in which calcification was seen in adnexal disease originating in carcinoma of the cervix had marked radiation changes in the pelvis. She subsequently required ileocolostomy and external colostomy for bowel obstruction secondary to radiation ileitis and proctosigmoiditis.

With the exception of Cases 5 and 11, all the patients were under 40 years of age. The preponderance of young patients in this small series agrees with the experience of others who found that calcification in certain groups of malignant tumors is generally found in the younger age groups.[5]

ROENTGEN APPEARANCE

In those cases in which the calcium was demonstrated at its inception, it was seen

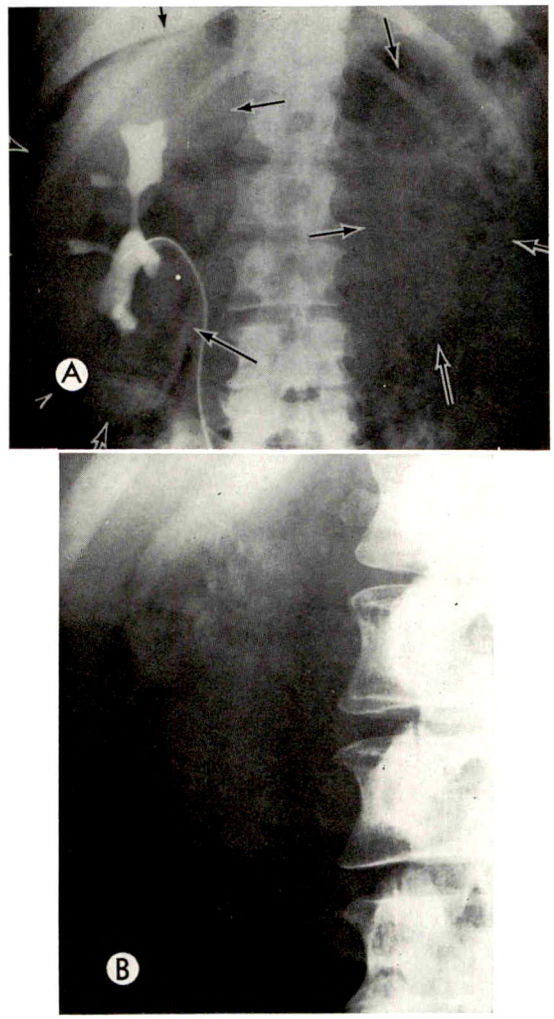


Fig. 7. Case 5. Lymphocytic lymphosarcoma with infiltration of the right kidney. (*A*) Retrograde pyelogram before therapy. Right kidney measures 24.5 cm. in its vertical axis, left measures 14.0 cm. (*B*) Post therapy pyelogram showing shrinkage to 12.5 cm. and deposits of calcium.

to take the form of fine, punctate deposits scattered in an irregular fashion in the tumor. On occasion, short thin streaks no more than a millimeter or so in length were seen. As the amount increased the granules became coarser and in some instances formed a roughly circular structure 2 mm. or so in internal diameter. Later, coarse plaques and streaks and larger irregular deposits formed. Sometimes, shell-like calcification was seen at the periphery of the neoplasm. In most cases, irregular portions of the affected mass were spared. As the tumor shrank, the calcium concentration naturally became greater and the deposits denser on the roentgenogram. In none has the amount of calcium diminished.

DISCUSSION

There has been little written about the changes in neoplastic tissue following therapy, particularly irradiation. However, these are generally found to be such as to favor degeneration and necrosis, particularly at therapeutic dosage levels. Besides cellular necrosis which results directly from radiant energy, the blood supply is severely compromised by the vascular damage, especially to endothelium, which is most evident at the capillary level. Reparative attempts usually give rise to fibrosis which may contribute further to degenerative and necrotic changes. It is in this milieu of degeneration, necrosis, and perhaps hemorrhage that calcification appears.

The *de novo* calcification observed in tumors and reported by many authors usually follows the various types of degeneration, hemorrhage, and necrosis;[9] an exception is the psammomatous calcification which is found in malignant epithelial cells.[8] In studying carcinomas of the rectum, Engel and Dockerty[5] have observed calcium deposits in individual cells and in the mucus produced by these tumors; more often they are found in areas of necrosis. Dystrophic calcification, which includes the majority of tumor calcification, has as its most important causative factors (1) local tissue degeneration and (2) impoverished blood supply. In all instances in which this occurs, the vitality of soft tissues is depressed by previous disease or senescence.[11] A local stimulus enabling or encouraging vicarious calcium deposition in degenerating and necrotic areas has been offered as an explanation, since it has been said that excessive concentration of calcium, local or general, is not involved.[7] However, some investigators feel they have shown that a local excess of calcium may indeed be a factor, having been demonstrated in conjunction with a deficiency of potassium in slowly growing, old or necrotic tumors. Beebe[1] states that the amount of calcium in such tumors may be 10 times that in vigorously growing neoplasms without degenerative change. Clowes and Frisbie,[2] in an experimental study of mouse tumors, came to the same conclusion. Necrotic and even necrobiotic tissues have an extraordinary capacity for taking up calcium, though no adequate explanation of the mechanism of calcium deposition can as yet be given.[10] Ewing[6] states that a special predisposition to calcification may exist in certain instances, but this latter statement cannot be considered as related to all of the 15 cases discussed above, so far as we are aware. It is surprising that calcification of the type described does not appear with greater frequency; radiation is a very commonly utilized therapeutic agent, often with dramatic decrease in tumor size. Yet a review of the roentgenograms of several hundred patients who had had excellent response to radiation therapy (in the sense that shrinkage of tumor occurred) revealed no further cases.

Calcification has also been noted in breast tumors following radiation therapy.[4] The deposits seen are coarse and irregular on occasion, and are presumably of the same nature as those discussed.

The only allusion to the appearance of calcification in tumor in response to therapy was found in a textbook of diagnostic radiology.[11] An illustration of a sacrococcygeal chordoma is reproduced, and the legend states that the tumor, though initially without calcification or trabecula-

tion, developed calcified areas following roentgen therapy. Despite this, the tumor continued to enlarge with progressive sacral destruction.

There are some case reports dealing with tumors already showing calcification to which radiation was administered. In one of these[3] diminution in the calcification occurred following therapy; this resorption the authors interpreted as indicating a favorable response. If, as Ewing believes, the psammomatous type of calcification is a part of active growth, this attitude is reasonable. Another case[8] is reported as showing an increase in density following irradiation, but the author attributes this to increased concentration of calcium in the tumor consequent on decrease in size, rather than to the appearance of new deposits.

SUMMARY AND CONCLUSIONS

Fifteen cases are discussed in which calcification appeared in neoplasms following therapy. Thirteen were subjected to irradiation and 2 to chemotherapy. The calcific deposits are of the coarse, irregular type seen in dystrophic calcification occurring in necrotic tissue. In 3 cases studied histologically, the calcium was seen to be located in or near areas of degeneration and necrosis. This uncommon finding should pose no differential diagnostic problem to the roentgenologist aware of its existence.

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ADDENDUM

Since this article was submitted for publication, a sixth patient (Case 4) has come to autopsy. This confirmed the presence of the partly calcified mass arising in lymph nodes near the upper border of the pancreas. There were large areas of necrosis and fibrosis in the enlarged lymph nodes within which the calcium was deposited. There was no recognizable pattern to the calcium deposition, other than that it occurred predominantly in necrotic tissue. Microscopic calcification occurred in other degenerating retroperitoneal lymph node disease, but was not in sufficient quantity to be appreciated roentgenographically. Residual Hodgkin's disease was present; certain areas were suggestive of reticulum cell sarcoma.

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THYROID CANCER FOLLOWING IRRADIATION FOR MEDULLOBLASTOMA*

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THE present report concerns 2 children who received roentgen therapy for medulloblastoma and subsequently presented with thyroid cancer. We found no other reports of this sequence, and only 3 other cases of thyroid cancer in patients given radiation treatment for malignancy.

REPORT OF CASES

CASE 1. The patient, W. S., was admitted to the Children's Hospital of Buffalo on September 23, 1949 at the age of $4\frac{1}{2}$ years with a 4 month history of vomiting and staggering. Physical examination disclosed an irritable white male with a large head which was tympanitic to percussion. He had a slight internal strabismus of the left eye. There was marked papilledema. He also showed ataxia and dysmetria in the left arm and both legs, while in the right arm there was more a tremulous unsteadiness than ataxia. Tendon reflexes were hyperactive throughout and Babinski signs were present bilaterally. A roentgenogram of the skull showed marked separation of the sutures and some enlargement of the sella turcica.

An occipital craniotomy was performed on September 29, 1949. Over the medial raphe of the cerebellum, several small pearly white nodules of tumor tissue were found measuring 1 to 2 mm. in diameter. An incision was made in the cerebellar hemisphere and at a depth of 3 cm. a very soft grayish-pink tumor tissue was encountered. About 30 cc. of the tissue was removed. Histologic examination of these sections of tumor and arachnoid was made by Dr. Kornel Terplan, Professor of Pathology at the University of Buffalo, and was reported as follows: "Immature glioma with numerous mitotic figures and slight nuclear disintegration. The general pattern points to medulloblastoma: Only rare pseudo-rosettes . . . very distinct infiltration by tumor cells in the arachnoid" (Fig. 1).

The patient received 37 roentgen treatments from October 3 through December 29, 1949. Right and left lateral 20×20 cm. and an occipital 10×15 cm. skull ports were used. The dorsal and lumbar spine were treated alternately through a single posteroanterior 5×20 cm. port. The factors were 200 kv., 15 ma., 50 cm. target skin distance, half value layer 0.9 mm. Cu. At each treatment a skin dose of 200 r was delivered to one skull port and one spinal port. The patient was given a total skin dose of 3,000 r to both lateral skull ports, 2,800 r to the occipital skull port, and 2,200 r to each spinal port. It was later calculated that the thyroid received approximately 2,000 r.

Symptoms of vomiting and ataxia recurred in April, 1950. Additional roentgen therapy was given from April 29 through May 23, 1950, using 2 skull ports and 2 spinal ports. The factors were the same as before. The right lateral skull received a total skin dose of 1,600 r, the left lateral skull port 1,800 r, the dorsal spine 1,600 r, and the lumbar spine 1,800 r. The dose to the thyroid from this course was subsequently estimated to be about 1,000 r. He also received 4 daily doses of 1.8 mg. of nitrogen mustard intravenously from May 15 through May 18, 1950.

He was symptom free for approximately 7 years. On routine follow-up examination on July 5, 1956 the right lobe of the thyroid was noted to be enlarged with a definite olive-sized nodule in the upper pole of the right lobe. A right hemithyroidectomy and block dissection of the right anterior cervical lymph node chain were performed. The thyroid lobe on section was found to be mostly replaced by grayish-white tumor tissue. This diagnosis by Dr. Terplan was: "Solid parenchymatous tubular carcinoma of the thyroid of the so-called proliferating struma type of Langhans." There was venous invasion and lymph node metastasis. (Fig. 2).

As of July, 1961, the patient was well without recurrence of thyroid or cerebellar neoplasm.

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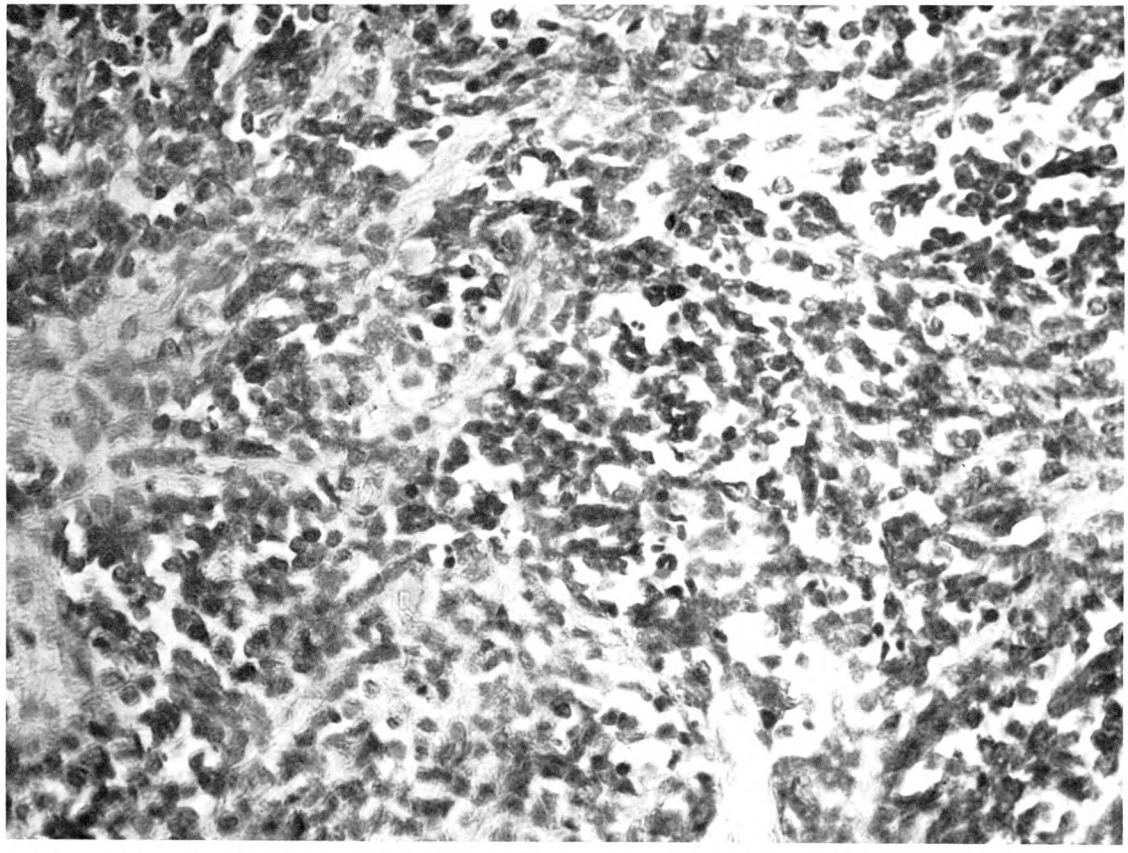


FIG. 1. Case I. Medulloblastoma removed at the age of 4 years. (H. & E. × 184+X2).

His only neurologic deficit was moderate optic atrophy bilaterally.

CASE II. The patient, R.M., was admitted to the Children's Hospital of Philadelphia on January 17, 1949 at the age of $7\frac{1}{2}$ years with a $1\frac{1}{2}$ year history of headache and vomiting. The significant physical findings in this white female were bilateral papilledema and an ataxic gait.

On January 19, 1949, a suboccipital craniotomy revealed a large reddish solid tumor arising from and completely filling the fourth ventricle and extending down to the level of C1. This was partially removed, the aqueduct unblocked, and a cannula inserted.

Dr. F. H. Lewey gave the following pathologic report: "It is a cellular tumor consisting of small cells with almost naked irregular outline and carrot-shaped nuclei rich in chromatin. These cells are arranged in typical pseudorosettes or in parallel rows, or around or along a central blood vessel." Dr. Lewey further commented upon the scantiness of blood vessels and absence of reticulin and collagen, and upon a prominent network of glia fibrils. His diagnosis was medulloblastoma, gliofibrillary (Fig. 3).

Roentgen therapy was given from February 5 to April 4, 1949. The skull was irradiated through a right lateral, a left lateral, a direct posterior, and a superior portal over the vertex, each measuring 7×7 cm., and 2 additional portals spanning the entire spinal column. The factors were 200 kv., 15 ma., 50 cm. target skin distance, half value layer 1 mm. Cu. Each portal received approximately 2,000 r measured in air. The thyroid dosage was not calculated and the physical measurements of the patient were not recorded, but it may be roughly estimated that the thyroid probably received at least 2,000 rads in this treatment course. From May 1 to June 14, 1949 the skull portals were given another course of treatments totaling about 1,550 r in each area. This may have added another 1,000 rads to the thyroid.

The patient remained well until at the age of 18 a routine insurance examination at her place of employment disclosed nodular enlargement

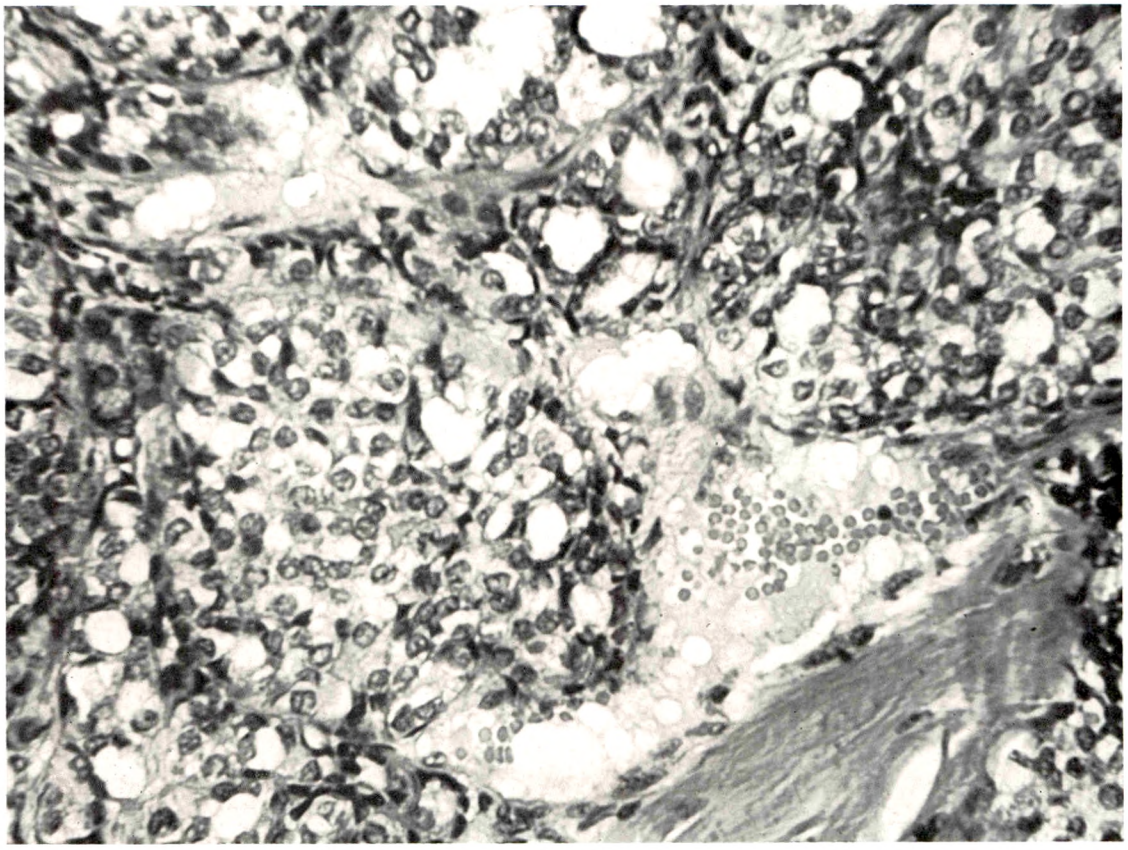


Fig. 2. Case 1. Thyroid carcinoma resected at the age of 11 years. (H. & E. × 184+X2).

of the thyroid. A tracer dose of radioactive iodine was given on February 23, 1960. The 24 hour uptake in the neck was 20 per cent and scintillation scanning revealed a normal-appearing right thyroid lobe, but only 2 small areas of uptake in the left lobe, and no uptake in 2 palpable nodes beneath the left sternocleidomastoid muscle. A left thyroid lobectomy was performed on March 7, 1960. The tumor was fixed to the trachea, carotid sheath, and strap muscles, and could not be completely removed. Dr. John Moran described the histology as "highly anaplastic, poorly differentiated papillary carcinoma of the left lobe of thyroid" (Fig. 4).

At a second operation on April 17, 1960 the right thyroid lobe was removed. A tracer dose of I^{131} was given preoperatively for autoradiography, but no tumor was found in this specimen, which was reported as non-toxic nodular goiter. Scintillation scanning 4 days after this operation showed only 2 very small areas of uptake in the left side of the neck. Thyroid replacement medication was withheld, and after an interval of 5 weeks another I^{131} tracer dose was given. The 24 hour uptake in the neck was 16 per cent, and the scintillation scan showed multiple areas of uptake in both sides of the neck. It was inferred that endogenous thyroid-stimulating hormone had promoted function of either multiple areas of tumor, multiple fragments of surgically-disseminated thyroid, or both. A 100 mc treatment dose of I^{131} was given. The apparent 24 hour uptake in the neck was 27 per cent, but 88 per cent of the treatment dose was excreted in the urine in the first 48 hours. Scintillation scanning, done 2 weeks after the treatment dose, again showed multiple areas of uptake in the neck.

After 4 months, definite clinical signs of hypothyroidism had developed. A tracer dose of I^{131} showed only 2 per cent uptake in the neck at 24 hours, interpreted as possible functioning tumor since the scintillation scan showed it to be distributed bilaterally in several areas. Another 100 mc treatment dose was given, with 2

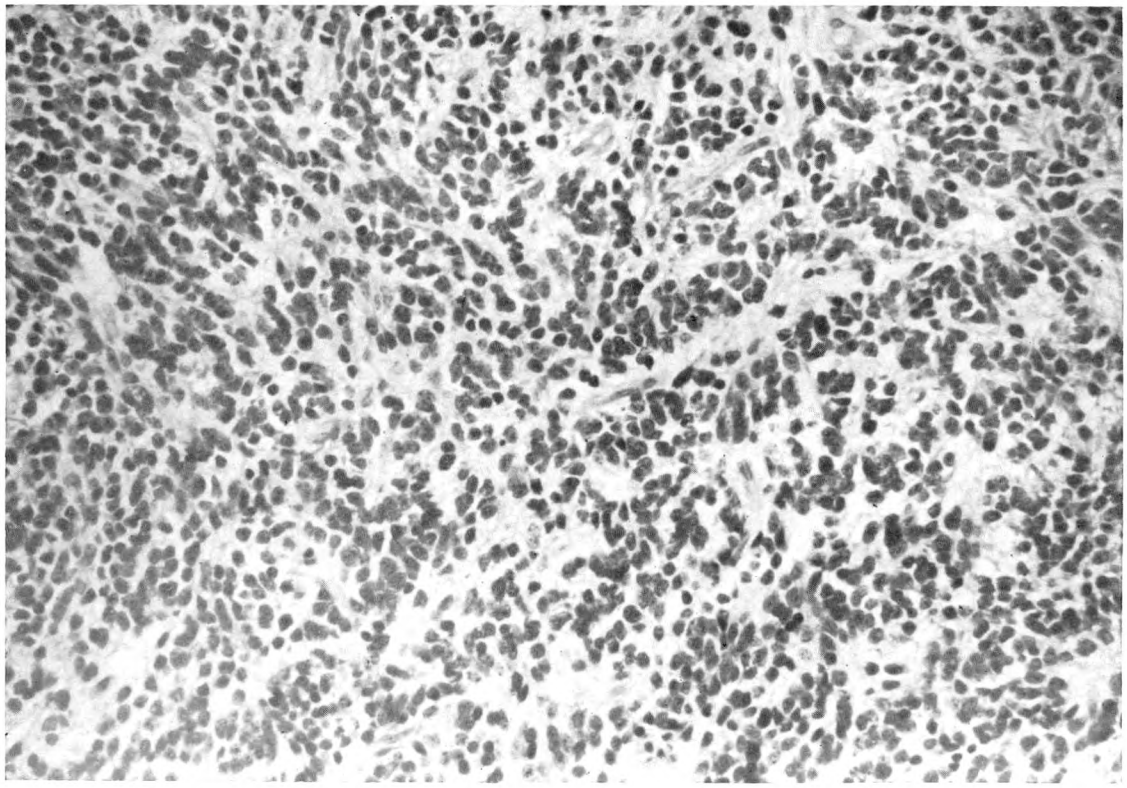


FIG. 3. Case 11. Medulloblastoma removed at the age of 7½ years. (H. & E. × 195).

per cent neck uptake in 24 hours and 85 per cent urinary excretion in 48 hours. A scintillation scan pattern after 8 days closely resembled the tracer dose distribution. Shortly after this, the patient was placed on thyroid USP which was gradually increased to 5 gr. daily. In December of 1961 she was in apparent good health although the 2 small nodules in the left side of the neck noted before the first thyroid operation were still present.

DISCUSSION

We have found reports of 285 cases of thyroid carcinoma in persons having a history of radiation therapy to the neck. Winship and Rosvoll[27] collected 221 of these, all diagnosed histologically before 15 years of age. Nearly all of the remaining cases reported [1,2,3,5,6,7,9,10,14,16,18,19,20,22,24,25,26] were under the age of 25 years.

The ages of the reported cases suggest that thyroid carcinoma following irradiation is almost exclusively a problem of childhood. However, as discussed elsewhere,[18] the likelihood of recognizing an association between irradiation and thyroid cancer is probably much greater when both occur within childhood. There is direct evidence that the adult human thyroid is not completely insensitive to irradiation. Lindsay *et al.*[12] found distinct pathologic changes in normal adult thyroid glands that had been subjected to intensive irradiation incidental to therapy of adjacent structures. In glands which were initially hyperplastic, they found changes suggesting a precancerous state. The lifetime histories of adult thyroid carcinoma patients should be searched meticulously for exposure to ionizing radiation. The search should extend back to infancy, as it is of interest to determine both whether irradiated adults get thyroid cancer and whether irradiated children get thyroid cancer after they become adults.

Three of Winship and Rosvoll's[27] cases were irradiated for malignant neoplasms: 1

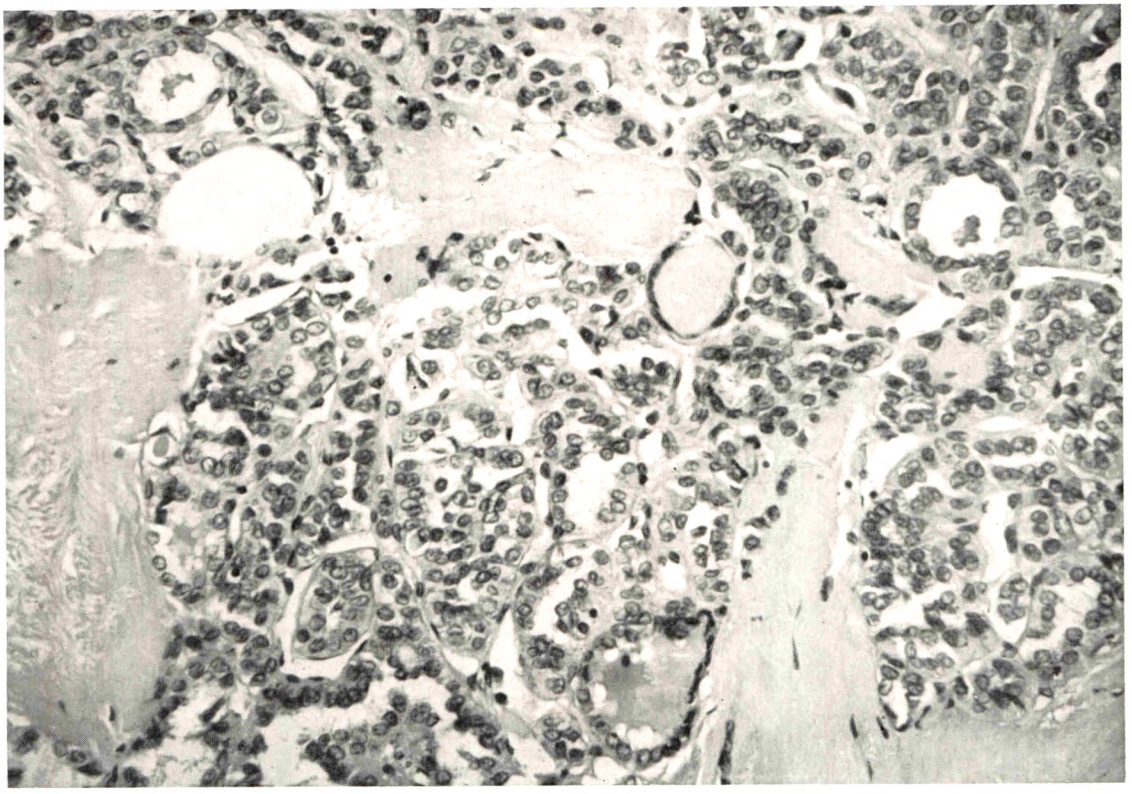


Fig. 4. Case 11. Thyroid carcinoma resected at the age of 18 years. (H. & E. × 195).

astrocytoma treated with the clinical diagnosis of medulloblastoma,[13] 1 lymphoma[17] and 1 retinoblastoma. With our 2 cases, this brings the total number of thyroid carcinoma cases with previous irradiation for malignancy to 5, as compared with 282 cases with history of irradiation for benign conditions, predominantly thymic enlargement. This ratio seems surprising, although it cannot be adequately evaluated in the absence of complete epidemiologic data on the incidence of irradiation for benign and malignant conditions, as well as on survival times after irradiation. Irradiation may be used much more frequently for benign conditions than for cancer, especially in childhood; both Lilienfeld[11] and Simpson[21] found evidence that more than 5 per cent of the juvenile population of one geographic area had received some kind of therapeutic irradiation.

The preponderance of patients treated for benign disease among the reported cases of thyroid carcinoma following irradiation might also be related to differences in the technique of irradiation. When radiation therapy is given for malignant tumors and the thyroid happens to lie in the direct beam, it will usually receive up to several thousand rads within a few weeks, with exposures approximately every day. If the thyroid is not in the direct beam, it will receive scattered radiation in much smaller dosage, but with a similar fractionation pattern. When radiation therapy is given for benign conditions such as thymic enlargement, the total dose is usually only a few hundred rads, generally given in a few exposures which are often separated by several days or weeks.

The differences in radiation dose and timing might be important. Numerous investigations in animals have shown these factors to have a complicated relationship to carcinogenesis.[23] In rats, thyroid tumors are induced quite effectively with low doses

of I^{131} but not with high doses.[4,15,23] Haran-Ghera *et al.*[8] found thyroid tumors in mice given 3 weekly doses of 150 rads total body radiation, and none in mice given 450 rads in a single session, but the number of tumors is not statistically significant. The point of these speculations is that radiation therapy details should be described fully in reports of suspected radiation injuries. From the accumulation of such data, it may ultimately be possible to define some of the dose-response relationships in radiation carcinogenesis for man.

More cases of human cancer following radiation exposure would almost certainly be discovered if a diligent inquiry for irradiation history were made whenever cancer is diagnosed.[18] The corollary of this fact is that carcinoma might be diagnosed earlier in patients with irradiation histories if more clinicians formed the habit of seeking such a history and allowing it to raise their suspicions of carcinoma, particularly of the thyroid gland. Both of the thyroid cancers reported here were discovered at routine examination, and were asymptomatic at the time of detection. The thyroid deserves particular attention in patients who have had irradiation of the neck, and nodularity should be surgically investigated.

SUMMARY

1. Two cases of thyroid carcinoma, appearing 7 and 11 years after therapeutic irradiation for medulloblastoma, are presented.

2. Only 3 additional cases of thyroid cancer following irradiation for cancer were found in the literature, as contrasted to 282 in patients treated for benign conditions.

3. At present, this sequence appears largely limited to children and young adults, but there is histologic evidence that the adult human thyroid is not invulnerable to irradiation. Further search may show irradiation histories to be more common in adult thyroid cancer patients than has so far been demonstrated.

4. The fact that the irradiation was given for benign conditions in nearly all the cases reported to have developed thyroid cancer subsequently is inconclusive in the absence of epidemiologic data on radiation therapy usage. However, analogies to radiation carcinogenesis in animal thyroid glands suggest that differences in irradiation technique, such as dose and time patterns, might play some part.

5. The problems discussed here indicate a need for more diligent search for irradiation histories in cancer patients, more critical examination of irradiated patients for possible neoplasms, and more detailed reporting of radiation factors in cases of suspected radiation injury.

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THE IMPACT OF IONIZING RADIATIONS ON THE EMBRYO AND FETUS*

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DUE to the necessary and proper increase in the use of ionizing radiations in both diagnosis and therapy (de Bellefeuille[1] 1961), it is natural that there will be increasing exposure of both recognized and unrecognized pregnancies (Payne[11] 1960). There are reports in the literature of some 32 or more congenital anomalies that have been attributed to prior x-irradiation of the human embryo or fetus (Rugh[14] 1958), but not one of these could be positively proven, although such anomalies have been experimentally produced in animals (Rugh and Grupp[15–20] 1959–1961). It may be some generations before enough human data are available to positively correlate the exposure of the embryo to ionizing radiations and certain sequelae. We are currently in the midst of a study to determine the effect of 1 r and 10 r on the rodent embryo with respect to the incidence of sterility, cataracts, ageing, and tumors and higher levels of exposure on the monkey fetus. Human data will always be complicated by the fact that about 5 per cent of human births are expected to show congenital anomalies. How many of these will ultimately prove to have been due to background radiation or other radiations is, at this time, mere conjecture (Wesley[29] 1960).

Permissible dose levels have been revised downward with each new consideration of the matter and in light of further knowledge (Stone[26] 1952). It is known from animal experimentation that both genetic and congenital effects may follow embryonic or fetal exposure (Carter[4,5] 1958–1960, Hicks[9] 1953, Rugh and Grupp[14–20] 1958–1961), so that it seems logical to recommend caution and maximum shielding when the gravid uterus may be involved. Genetic experiments with fruit flies are unconvincing to many clinicians until they learn that the rodent, much higher in the evolutionary scale, is some 14 times as radiosensitive as is the fly with respect to induced mutations (Russell[22–25] 1951–1956). One cannot extrapolate from the fly or mouse to the human, but one can postulate that the human, being also an animal, is probably similarly radiosensitive. The degree of sensitivity will have to await the accumulation of human data which may not take as long as we had feared, in light of current human genetic studies involving direct observations on chromosomes. During this interim, data from the rodent and the primate may well suggest for us the permissible levels for the human embryo and/or fetus.

During the last 5 years some 50,000 mouse and rat fetuses have been examined for x-irradiation effects, and since last year we have been able to crystallize much of our thinking about effects on the embryo. As with the human, such rodents have a normal base line of expectancy for early embryonic death and resorption, fetal death, and certain congenital anomalies. Above this base line of expectancy there is now no question but that penetrating ionizing radiations from 5 r upward can add permanent, irreparable effects to rodent embryos (Rugh[21] 1962). The effects are related to (1) the amount of irradiation, (2) the time interval over which the radiation is delivered, (3) the developmental stage of the embryo or fetus at the time of the exposure, and (4) the inherent genetic radiosensitivities of the forms studied.

Let us examine some of the major differ-

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Table I

MAJOR ABNORMALITIES FOUND IN THE MAMMAL (HUMAN, RAT, MOUSE) FOLLOWING FETAL X-IRRADIATION

Brain	Eyes	Skeleton	Miscellaneous
Anencephaly	Complete absence	Uniform reduction: stunting	Situs inversus
Porencephaly	Microphthalmia	Reduced skull dimensions	Hydronephrosis
Microcephaly	Microcornea	Vaulted cranium	Hydroureter
Encephalocele	Coloboma	Narrow head	Absence of kidney
Reduced medulla	Narrow iris	Cranial blisters	Degenerate gonad
Cerebral atrophy	Absence of lens	Spina bifida	Atrophy of lower extremities
Mental retardation	Open eyelids	Reduced and deformed tail	Cutaneous depigmentation and hyperpigmentation
Idiocy	Strabismus	Overgrown and deformed feet	Motor disturbances of extremities
Deformities:	Retinoblastoma	Digital reductions	Increased probability of leukemia
Narrow aqueduct	Hypermetropia	Abnormal limbs	
Hydrocephalus		Syndactyly	
Rosettes in cortex and medulla		Brachydactyly	
Dilatation of third and lateral ventricles		Odontogenesis imperfecta	
Neuroblastoma		Exostosis on proximal tibia	
Herniated brain		Metaphysis	
		Amelogenesis	

ences in the reaction of the embryo or fetus to ionizing radiations, in contrast with the adult stages into which the fetus develops. First, every stage of embryonic development is more radiosensitive than any postnatal stage by any criterion (Brent[2] 1960). The $LD_{50/30}$ ranges from about 16 to 60 per cent that of the adult, and the curve shows peaks of radiosensitivity. One of these, which results in frequent death, occurs at 10.5 days for the mouse and corresponds to about 28 days for the human. If the criterion of comparison is the incidence of gross congenital anomalies, this would be at 8.5 days for the mouse and approximately 24 days for the human (Rugh[14] 1958). Secondly, there is no such stage as *the embryo*, as there is for *the adult*. Rather, any embryo is a mosaic of innumerable radiosensitive areas associated with active proliferation of cells and differentiation into organs and organ systems, and this mosaic changes every minute. Thus, litter mates subjected to exactly the same physical

Table II

PREDICTIONS OF ULTIMATE INCREASE IN INCIDENCE OF CERTAIN DISEASES IN A POPULATION OF 150 MILLION WHEN THE RATE FOR DOUBLING "SPONTANEOUS MUTATIONS" IS 50 r AND LIFE-TIME (REPRODUCTIVE) ACCUMULATION IS 5 r (10 PER CENT) FOR THE POPULATION

Disease	Increase	Disease	Increase
Diabetes	75,000	Blindness	15,900
Congenital malformations	31,500	Deaf-mutism	4,500
Schizophrenia	20,700	Disseminated sclerosis	300
Manic-depressive	10,200		
Mongolism	3,600	Hemophilia	300

(Revised from Carter[4] 1958)



FIG. 1. Rat at 2 months of age showing differential reaction of the two eyes to whole embryo exposure to 100 r at 9.5 days. Microphthalmia of left eye caused by irradiation prior to the earliest indications of formation of the optic vesicles.

environment of ionizing radiations will exhibit a wide range of reactions, from death to apparent normality. Some of these variations may be due to inherent genetic differences, even within a single litter derived from the same parents. Therefore, it is unlikely that we will ever be able to designate any stage of development or dose level as "safe." Thirdly, the highly integrative nervous system takes its origin first, and rather early, but continues to make structural and functional connections with all subsequent organs and tissues as they develop. Thus, neuroblasts are found in the mouse embryo from 8 days continuously through the first postnatal days and probably in the human from about 16 days post conception until about 2 weeks after birth. These neuroblasts are so radiosensitive that they can be destroyed by 25 r (Hicks[9] 1953). The embryo or fetus, exposed at any time to 25 r can hence be expected to lose some of its neural connections, resulting in functional deficiencies. The organism can tolerate some cell loss and survive, but its functions will be impaired (Miller[10] 1960). Fourthly, there is no evidence that radiation-damaged embryonic cells can ever recover in the sense that they revert to the pre-irradiation condition. Whether one refers to genic, chromosomal, cytoplasmic, karyorrhectic, or pyknotic change, such cells are permanently and irrevocably altered. In contrast with the adult, who can replace or regenerate damaged tissue (as after epilation, erythema, or male sterility), the embryo cannot tolerate dead or grossly defective cells and hastens to eliminate them either by sloughing them off or phagocytizing them (Rugh and Grupp[15,16] 1959). Thus, we have adequate evidence that when any constituent cells of a developing embryo are radiation-damaged, the surviving embryo will be deficient to the extent of the damaged cells. This is the explanation of microcephaly, microphthalmia, brachydactyly, stunting, etc., which so often follow embryonic x-irradiation. Damage of one cell of a 2-cell early stage

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FIG. 2. Entire litter of delivered rats showing the effects of 100 r at 9.5 days. Every member much stunted and 5 out of 6 have gross cerebral anomalies.

FIG. 3. Entire litter of rats at 18.5 days' gestation showing every member with congenital anomalies, following 100 r at 9.5 days. Survival is impossible.

FIG. 4. Entire litter of hybrid mice exposed to x-rays at 8.5 days during earliest phases of neurogenesis. Hybrids, being heterozygous (as are most humans), exhibit wider range of congenital anomalies than do pure bred stocks. Every member is stunted, 2 exencephalies, and 2 resorptions. Every head is anomalous.

FIG. 5. Brains of rats at 2 weeks of age showing effects of 100 r delivered at 9.5 days. The control is to the left. Note asymmetry of both brains and slight hydrocephalic swelling.

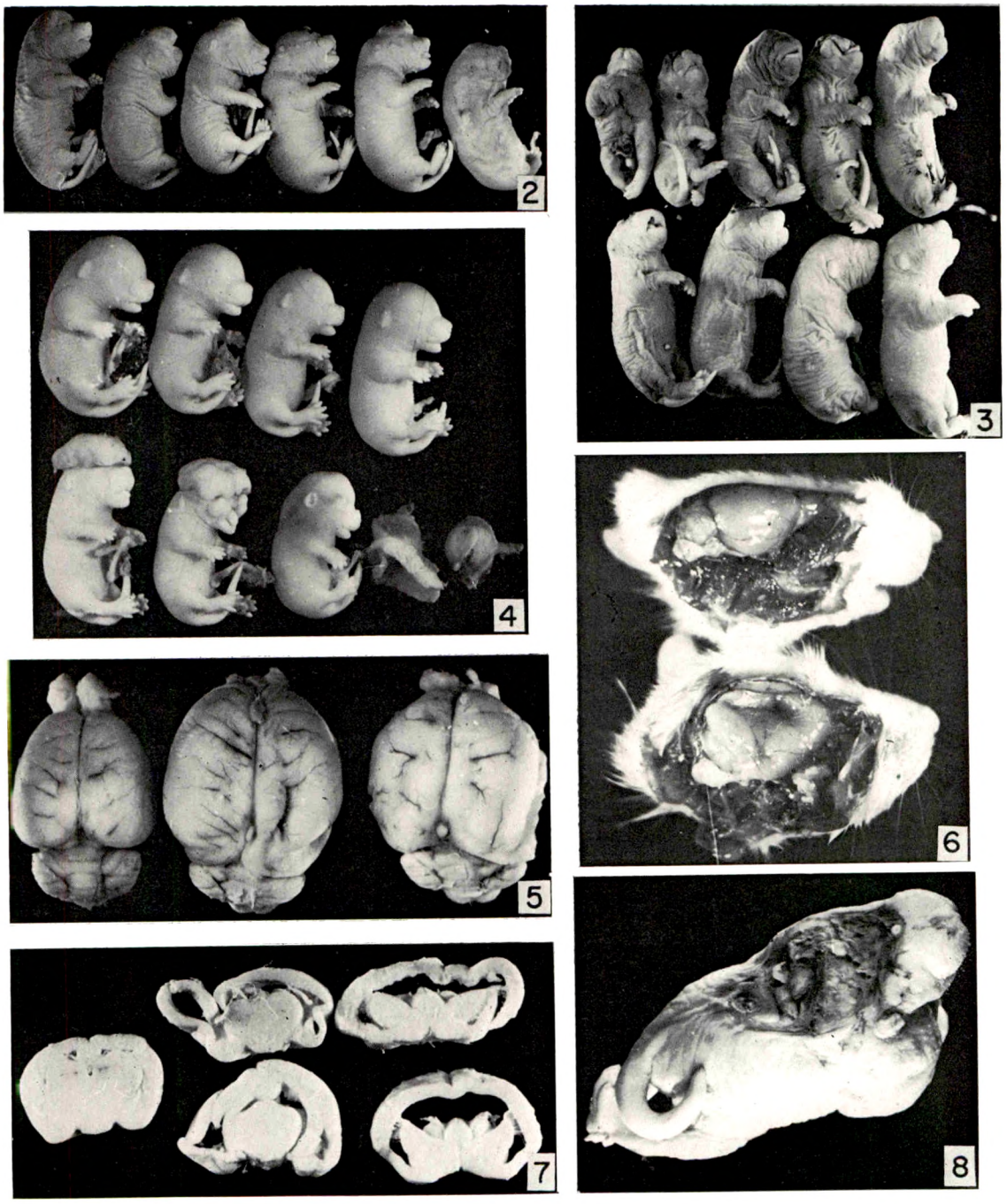


PLATE I

Fig. 6. Hemisected skulls of 2 rats at 2 months of age, the control above and the rat irradiated *in utero* below. Note hydrocephalus and partial collapse of irradiated brain.

Fig. 7. Gross sections of brains from a single litter of rats, taken at 2 weeks but exposed at 9.5 days to 100 r x-rays. The control of the same age is to the left. Note evidence of hydrocephalic swelling and expansion of cortex.

Fig. 8. Member of litter shown in Figure 3 with failure of both cephalic development and closure of the spinal cord and dorsal structures.

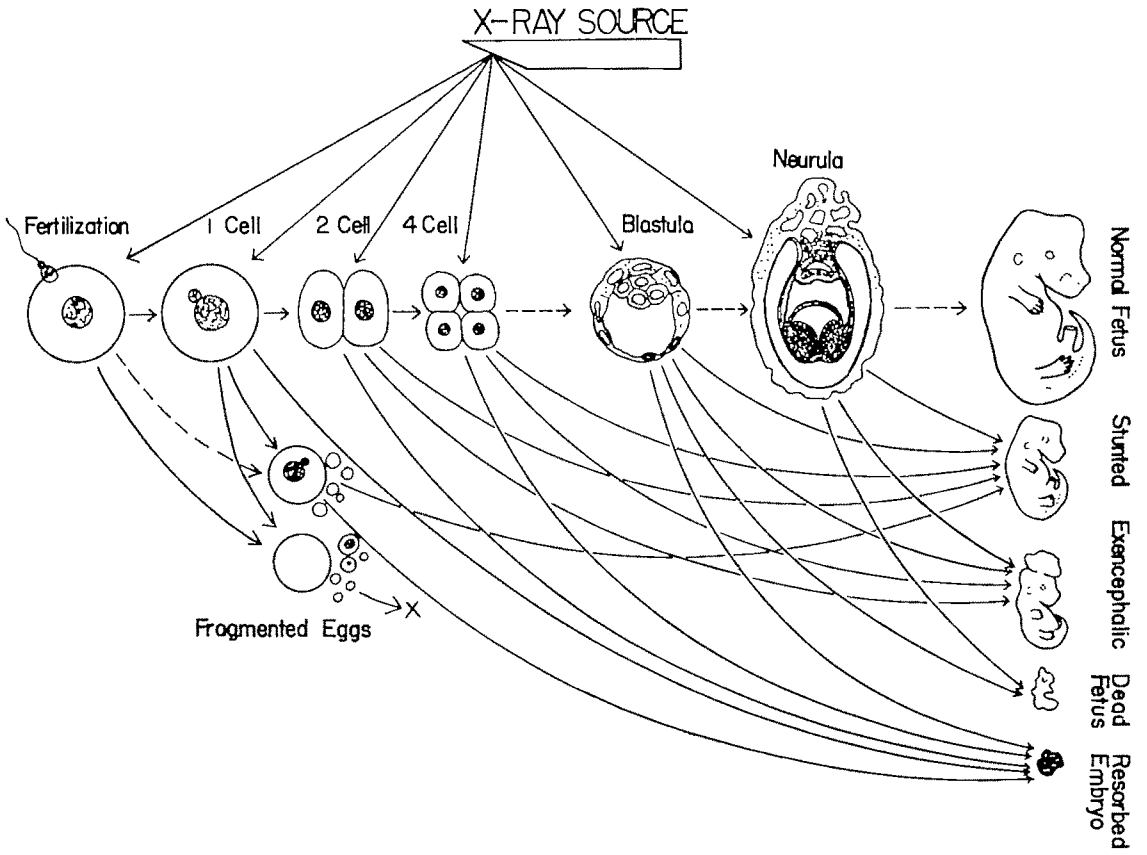


FIG. 9. Schematic drawing based upon irradiation studies with the mouse embryo and fetus. Note normal development from fertilization directly across to normal fetus. Irradiation insult may be delivered at various times but will have different effects. The neurula represents the development at 8.5 days, but congenital anomalies, stunting, and killing may result from irradiation at any of the earlier stages.

may have less congenital effect than comparable irradiation at a later stage because the embryo can eliminate the faulty cell and from the remaining totipotent blastomere derive a slightly reduced but otherwise normal individual. Fifthly, gross anomalies, generally designated as congenital, can be produced in embryos if they are irradiated prior to the completion of organ formation, but such anomalies can never be produced at any later stage. Thus, there are certain basic differences in the reactions of the embryo and the adult to ionizing radiations.

On the basis of comparable embryonic development, we can now designate certain periods in human gestation which might respond to irradiation insult by the development of congenital anomalies (Rugh[12,13,14,17,21] 1949–1962, Hicks[9] 1953, Rugh and Grupp[15,16,18–20] 1959–1961, Brent[2] 1960). For example, the *first trimester* in the mouse extends from conception to 8 days and corresponds embryologically to the first 20 days of the human. Because embryos during this period are comprised of relatively few cells, each cell is the more important because it is the progenitor of many eventual cells of the organism. Exposures of 5 r or more shortly after conception can kill, or if the cell survives, can cause congenital anomalies. Through the first several divisions of the normal egg, each resultant cell is equipotent and totipotent, which gives to this early embryo its unique ability to survive and develop into a

topographically normal individual. Each of its early undamaged cells could give rise to a complete individual, but when a maimed cell is retained, it interferes with normal development. Ionizing radiations are so minute and specific that single cells of an embryo may be damaged leaving others to carry on development. A maimed cell of a 2-cell stage which survives would normally give rise to approximately half of the cell population of the individual, possibly including the gonads. Thus, the cell might be better killed than maimed. The *second trimester* in the mouse, from 8 to 15 days, is the most radiosensitive with respect to the production of congenital anomalies by any means, and compares with the human gestation of 3 to 6 weeks. This is the period of most active organ formation, and 25 r can cause major central nervous system damage to the rodent. The *third trimester* in the mouse, corresponding in development to the human embryo after 6 weeks, is one in which gross congenital anomalies cannot be caused by irradiation simply because the organ systems have formed. However, throughout this period there are abundant radiosensitive cells in transition from the primitive to the histologically differentiated state, so that radiation insult results not in morphologic anomalies but in functional deficiencies (Miller[10] 1960, Werboff *et al.*[27] 1961).

It has long been known in experimental embryology that a destroyed cell can be eliminated from an early embryo and has little effect on development. Subjecting an embryo to ionizing radiations is like shooting it with an ultramicroscopic machine gun, some ionizations hitting some cells and bypassing others. A maimed cell, a cell with genic or chromosomal damage, which remains to try to differentiate can interfere with the normal morphogenetic processes and thus produce anomalies so that even 15 r at the 2-cell stage can cause cerebral hernia. When chromosomes are fragmented, broken, inverted, or when gene mutations are produced either in undifferentiated early embryonic cells or in germ cells and survive, these "mutations" are carried to all progeny cells. Thus, it may be wise in certain grave circumstances to consider allowing a gravid uterus to receive the full blast of irradiation rather than to give it only enough protection to allow the fetus to develop into a vegetative organism, or to recommend a therapeutic abortion.

Radiologists of Denmark have set up certain recommendations covering human fetal exposure. If a human embryo or fetus is exposed to x-rays of from 1 r to 10 r and if extenuating circumstances exist, a therapeutic abortion is recommended. In the event that such an embryo or fetus is exposed to 10 r or more, a therapeutic abortion is urged (Hammer-Jacobsen[7,8] 1961). This embryonic or fetal dose of 10 r may well be one to consider seriously. Estimates of the mutation-doubling dose to the gonads range from 30 to 80 r, and the current 30 year permissible whole body exposure level is 8 r. This permissible exposure is 10 per cent of the maximum estimated mutation-doubling dose, and if delivered to the gonads of all human fetuses would be expected ultimately to increase the incidence of heritable diabetes, for example, by about 90,000 in this country (Carter[4] 1958). One tends to be distracted by congenital anomalies from the fetal gonads which contain radiosensitive cells that may be the progenitors of long lines of descendents. Fallout is not the real hazard, since it accounts for an estimated 0.1 r in the next 30 years. The real hazards may be the natural background radiation in certain areas to which an embryo might be subject chronically for 9 months, or the unrecognized exposure of a gravid uterus in diagnostic radiology.

SUMMARY

1. During the first trimester in the rodent (0–7 days), which corresponds to the human period of the first 3 weeks, the rodent embryo is at its most sensitive stage in terms of dose and lethality, but not of anomaly production. Exposures of 5 to 15 r can kill the fertilized rodent egg and

can produce gross congenital anomalies of the central nervous system by maiming cells which are the normal progenitors of the nervous and other systems. Congenital anomalies are rare because damaged cells are eliminated and remaining cells can give rise to whole organisms (Brizzee *et al.*[3] 1961).

2. The period of highest incidence of anomaly production by ionizing radiations is about 8–11 days in the mouse and probably 20–30 days in the human. This is because such embryos are in their most active state of laying down their organ systems, with the maximum concentration of organ-forming cells in their most radiosensitive stage. Survival of irradiated embryos is better than at earlier stages, but as a result the production of congenital anomalies is much more frequent.

3. Following the completion of organogenesis in the embryo, ionizing radiations produce effects at the tissue and cellular level rather than at the organ level, so that gross congenital anomalies are not to be expected. However, at such times functional rather than morphologic effects can be expected, which would be revealed by electroencephalograms, electroretinograms, behavior and other intelligence effects. This period in the mouse occurs after the 15th day and in the human after the 6th week.

4. Fractionation of exposure lowers the incidence of particular anomalies but such embryos present a greater variety of anomalies due to insult at successive periods of critical sensitivity of different developing organ systems (Rugh and Grupp[15,16] 1959).

5. Since the embryo is a mosaic of differentiating centers, changing moment by moment, one cannot predict the results of x-irradiation insult. Within a single litter there may be vast differences in radioresponse due also to genetic variability so that a threshold for congenital anomaly production can probably never be established.

6. The basic effect of x-irradiation is the killing, or damaging, beyond recovery of the sensitive embryonic building blocks. Such cells are removed, often by phagocytosis, leaving a void. This void is filled, not by a compensatory spurt in growth or cell production, but by the re-shuffling and re-direction of undifferentiated cells so that some may fill the void both structurally and functionally. If the insult occurs late in development, such re-direction of potencies is impossible because undifferentiated cells are no longer available. In consequence, structural and/or functional anomalies may follow. When the insult occurs very early in development, the eventual fetus may be somewhat stunted but topographically quite normal, due to the still available undifferentiated cells which can be re-directed in morphogenesis.

7. Radiation-produced congenital anomalies should be regarded as expressions of loss or failure of certain structures to develop, rather than to the appearance of additional, new and grotesque structures. Some gross cellular changes caused by ionizing radiations are probably permanent, irrevocable, and irreparable, so that the organism as a whole rejects them and continues to develop without them if it can. This leads to losses which are most graphic when they involved the central nervous system (Brizzee *et al.*[3] 1961). Since the nervous system is all-pervasive, the completion of its development awaits that of other systems so that at all times in embryonic development there are some sensitive neuroblasts present. Specific organ deficiencies and anomalies are more frequent when exposure occurs at certain times, when those particular organs are actively differentiating. But it seems that the nervous system is peculiar in that its anomalies may result from exposure at any time from fertilization of the egg to the completion of development after birth. Damage to this central nervous system in late development may be revealed only by functional tests such as electroencephalogra-

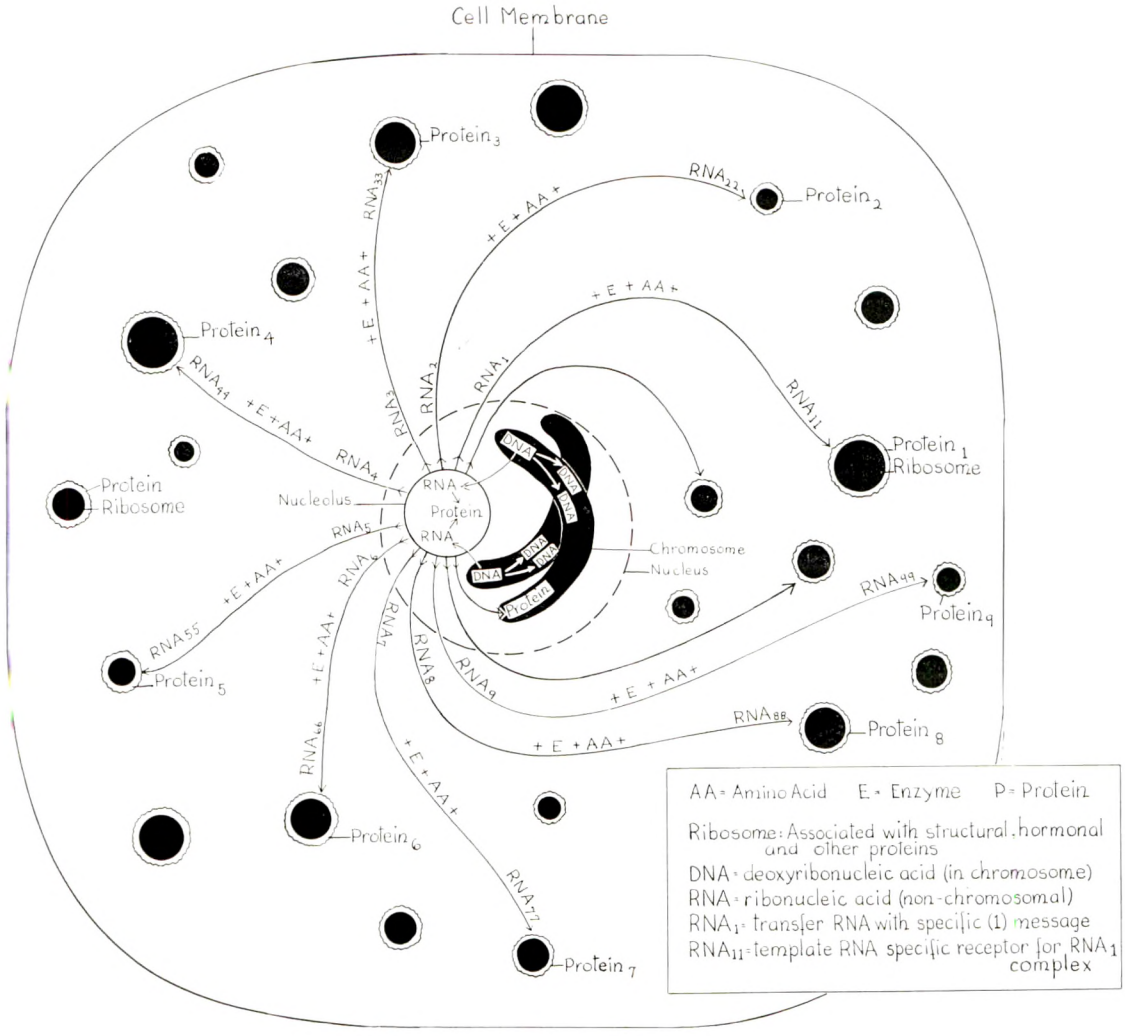


Fig. 10. Schematic representation of DNA-RNA relations in the synthesis of (morphogenetic) proteins in the cytoplasm of embryonic cells. Chromatin DNA derives the nucleolar RNA which, in interphase, diffuses throughout the cytoplasm to combine, as transfer RNA, with enzymes and amino acids to react with template RNA, associated with ribosomes, in the formation of specific proteins. There are many variations of RNA leading to the various proteins found in the large variety of differentiated tissue cells. Since DNA is particularly radiosensitive, this morphogenetic synthesis, hence differentiation, is prevented and the cell either dies or becomes anomalous.

phy, electroretinography and psychologic behavior and I. Q. tests.

8. The synthesis of specific proteins from free amino acids is the central theme of all biologic growth and differentiation. A radiation-damaged abnormal nucleus prevents this synthesis and thereby prevents normal morphogenesis when the cell is allowed to survive. Thus, since the DNA of the nucleus is so highly radiosensitive, the seat of radiation damage to the embryo or fetus is probably the cell nucleus, and specifically the chromatin DNA molecule. This molecule is the bearer of genetic information which leads to cell differentiation so that, when it is damaged, cell, tissue and organ anomalies may follow. For this reason, the few cells of the very early em-

bryo, the progenitors of all cells of the fetus, should be protected against x-radiation insult at all cost (See Fig. 10).

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NEWER CONCEPTS OF RADIOTHERAPY*

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IN SPITE of the great progress which has been made in recent years, the only known means by which cancer can be cured is by surgery or radiotherapy, used singly or in combination. Neither surgery nor radiotherapy *per se* will provide the ultimate answer to the cancer problem.

Probably some agent or agents used singly or in combination which, when introduced within the body will selectively seek out and destroy the cancer cells without causing irreparable damage to normal cells, will be the answer. The effectiveness of such an agent or agents may be greatly enhanced when used in combination with either surgery or radiotherapy. It is quite possible that various types of agents and/or combinations of these agents may have to be developed for the treatment of each of the many different types of cancer. The cancer problem represents a multiplicity of diseases with multiple factors active in its causation.

Without question cancer is of concern to everyone. Approximately 1 in each 4 individuals will develop cancer during their lifetime. One out of each 3 cancer patients is now being cured, and it is certainly possible to cure 1 of every 2 cancer patients by means of the diagnostic and therapeutic methods now available. Approximately 500,000 new cancer cases are diagnosed each year, and with the continued increase in the population, this figure will steadily increase.

A great deal of effort is being exerted in attempts: to find a simple blood test for the diagnosis of cancer before symptoms have occurred; to find the possible association of viruses in human cancer as a causative factor; to find out why some patients never develop cancer; why spontaneous disappearance of the cancer cells occurs in some cancer patients; how to increase the radiosensitivity of cancer cells; what causes the cancer cells to develop, and if it can be determined when the transition takes place from the noncancerous to the cancerous state.

The discovery of the roentgen ray has been a tremendous boom to the great progress being made in the field of medicine. In the past few years with the advent of the fallout from atomic weapons testing, the general population has become acutely aware of the potential dangers resulting from the injudicious exposure to ionizing radiation.

POTENTIAL RADIATION HAZARDS

The improvements continually being made in radiologic techniques, the use of proper shielding, the periodic testing of the equipment, and the use of ionizing radiation only by competent individuals will provide adequate safeguards. Under the conditions just mentioned, no individual should be denied roentgenographic examinations on the basis of possible harmful effects because the information obtained will far outweigh any potential harmful effects. At the very outset, however, I wish to state that in this discussion we are concerned with the direct somatic effect of radiation to the individuals treated for malignant disease, and not with the health hazards and possible genetic effects of ionizing radiation. The radiotherapist treats very few benign lesions. He has for the most part a much older patient group in whom reproductivity is a decreasing factor. He is mainly concerned with cancer and he usually utilizes filtered, coned radiation with higher kilovoltages directed to relatively small localized areas of the body.

* Presented at the Sixty-second Annual Meeting of the American Roentgen Ray Society, Miami Beach, Florida, September 26–29, 1961.

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RADIATION PHYSICS

Recently there has been a growing impression that the diagnostic radiologist must learn as much as possible about radiation physics and radiation biology and that information disseminated in these areas should not be emphasized only to those who plan to do radiation therapy. Perhaps this stimulus has been triggered by the public clamor about the potential health hazards of diagnostic radiologic procedures, the possibility of a nuclear war with the exposure of great numbers of the population to "fallout," and with radiation problems associated with space travel. Also, by the excellent improvements being made in radiographic equipment and techniques and by the realization that these improvements are but a few of the many better things awaiting to be developed or perfected.

PROGRESS IN RADIOTHERAPY

When one thinks in terms of the newer concepts of radiotherapy, one must be fully aware of the continual advances which have been made through the accumulation of experience and the refinements made in technique and dosimetry since the discovery of the roentgen ray in 1895 by Röntgen and of radium by the Curies in 1898. Radiotherapy has had a tremendous salutory effect on the cancer problem during the past 60 odd years.

Boland,[2] as well as others, have found that, although the same equipment was used in the treatment of certain types of cancer, increased knowledge, better patient care, and improved techniques have produced better results. Boland noted, for example, a progressive improvement over a period of years in the results following the treatment of carcinoma of the cervix at Christie Hospital and the Holt Radium Institute. From 1933 through 1938 the 5 year survival rate for all stages of cervical cancer treated by radiotherapy was 28 per cent; from 1939 to 1944, 36 per cent survived 5 years; from 1945 to 1949, the survival rate was 42 per cent. During a 12 year period, the 5 year survival rate increased 50 per cent.

It used to be thought that cancer was an autonomous new form of growth which recognized no control by the body. In recent years, it has been more fully recognized that certain tumors are partially hormone dependent and are not entirely free of endogenous control. For example, some tumors of the breast, prostate, and ovary fall into this category. Because of the special metabolic characteristics of these tumors, definite palliation can be obtained by means of radiation or surgical castration and adrenalectomy or by surgical or radiation hypophysectomy for breast cancers, by hormone therapy and orchidectomy for prostate cancer, and the use of chemotherapy for ovarian cancer. Radiotherapy is usually always of considerable value in addition to its curative qualities where only palliation is desired.

THE EDUCATION OF THE RADIOTHERAPIST

It is encouraging to note a definite trend in this country toward the establishment of straight radiotherapy training for those who wish to become radiotherapists rather than have combined training with diagnostic radiology. For example, in California the University of California School of Medicine, San Francisco, the Stanford School of Medicine, and the University of California at Los Angeles, School of Medicine have already begun straight radiotherapy residencies of 3 or more years' duration or plan to do so by July, 1962.

In certain European countries, for many years the training of the radiotherapist has been separate from that of the diagnostic radiologist. In many instances, the radiotherapist was a trained surgeon or internist before taking up the specialty of radiotherapy. Because of the excellent over-all training of these radiotherapists, they have enjoyed the respect of their colleagues and have enhanced the value of this specialty. A surgeon should not operate just because he has a knife, the internist should not merely dispense pills nor the radiotherapist use ionizing radiation just because he has it available. Unfortunately, too often

this is the case. The proper treatment for the patient should be selected and the successful outcome will depend upon the type of treatment selected by the first physician who treats the patient.

Thorough training in radiation physics, radiobiology, pathology, knowing the life history of cancer, the recognition of complications occurring during treatment, the value of chemotherapy, and knowing when other methods of therapy may be superior in the treatment, for example surgery in some cases, is most important. The selection of well motivated individuals with an insatiable desire to obtain knowledge and then to provide them with an opportunity to learn and a considerable variety of clinical material is essential to the success of a straight radiation therapy program. There is certainly a shortage of well trained radiotherapists in this country.

I know of no specialty in which teamwork is so desirable because the successful treatment of cancer requires the best of cooperation between the surgeon, the pathologist, radiotherapist, internist, gynecologist, dermatologist, radiation physicist, and of all other specialists. It is exceedingly difficult for one individual to be proficient in all branches of medicine. It also must be frustrating for a busy radiologist to try to encompass all the subspecialties of this most important field of medicine. There has been a recent trend for more cooperation between surgeons and radiotherapists, particularly since the more common usage of supervoltage therapy.

The radiotherapist is usually provided with many opportunities both to cure and to palliate cancer. He must be aware of the possible complications which may occur and he must adequately treat the early lesions, knowing that he will incur some complications as a calculated risk. Above all, the radiotherapist must be a physician trained in the problems associated with the general care of the patient, in the use of antibiotics, transfusions, proper diet, and in the recognition for the need of certain supportive measures. There is more tendency at the present time to treat a patient with cancer rather than to just treat the cancer and ignore the patient's over-all problems.

With the continuing trend toward the use of supervoltage therapy, which is very expensive and requires more space and greater protective shielding, there may be more concentration in the future of cancer patients in various centers about the country. Where supervoltage equipment and research facilities are available, there should be a full-time radiation physicist and a radiobiologist. Kaplan,[18] Buschke,[3] and others have pointed up the need for the establishment of radiotherapy centers in this country.

The modern radiotherapist is better trained. Now more than ever, research is encouraged in the graduate educational program which is so set up that the graduate student can do one or more research projects of his own choosing. Everything possible is done to keep alive and fan the spark of curiosity which makes the graduate student strive for a better understanding of disease and of his patients. It is fully appreciated that many diagnostic radiologists are very capable radiotherapists and that for some time in this country the major load of radiotherapy will be done by radiologists trained in both diagnostic and therapeutic radiology.

There have also been improvements in the quality of teachers in the medical schools. Snapper[29] has stated that "The teachers who are charged with the training of young medical graduates must be clinician-scientists, *i.e.*, they must have, apart from their scientific orientation, a healthy respect for that part of medicine which is empirical in nature and is based on experience."

CHEMOTHERAPY

One of the most promising developments in the treatment of cancer has been in the field of chemotherapy. Much progress has been made since World War II with the introduction of nitrogen mustard (methyl bis [B-chloroethyl] amine hydrochloride). Later, many other related nitrogen mustard

compounds as well as other chemotherapeutic agents were produced.

Some of the drugs which are currently being used in this country are chlorambucil (Leukeran), amethopterin (Methotrexate) and methotrexate with citrovoram factor for intraarterial infusion for carcinoma of the head and neck, 6-mercaptopurine (6MP, Purinethol), 5 fluorouracil (5-FU), triethylenethiophosphoramide (TSPA, Thio TEPA), triethylene melamine (TEM), busulfan (Myleran), mitomycin C, actinomycin D, vinblastine sulfate (Velban), uracil mustard (U-8344), and cyclophosphamide (Cytoxan, Endoxan). The steroids and hormones which have increased our knowledge of cancer and helped considerably in palliation must also be considered as chemotherapeutic compounds.

Many of the chemotherapeutic drugs are quite toxic, are used for palliation only, and should always be used under careful supervision. The injudicious use of these drugs by the untrained will not only be detrimental to the patient but may slow down their potential growth as a cancer weapon.

It is important to know which of these drugs may enhance the radiosensitivity of cancer cells. The combination of radiation therapy with certain chemotherapeutic drugs has produced better palliation in some types of cancer. Reese *et al.*[25] and Bagshaw[1] have pointed out the value of triethylene melamine (TEM) as a potentiator when used in combination with radiation therapy in the treatment of retinoblastoma. Hall *et al.*[17] have mentioned the potentiating effect of 5-fluorouracil used with radiation therapy and D'Angio *et al.*[7] that of actinomycin D. Farber[9] summarized the results in the treatment of 29 patients with Wilms's tumor who received actinomycin D intravenously and concomitant radiation therapy, and found that 35 per cent of the cases were living with no demonstrable evidence of tumor from 10 to 35 months from the time of the onset of symptoms. The combination of two or more chemotherapeutic drugs may produce palliation where either one given alone would prove of no definite value.

The perfusion technique for the use of chemotherapy in the treatment of cancer was first described by Klopp and his associates[20,21] in 1950. In 1957, Ryan, Winblad, Krementz and Creech[26] improved the technique and reported the use of perfusion with an extracorporeal circuit. By this localized perfusion technique, from 6 to 8 times the maximum systemic dose may be given under higher oxygen tension and with protection to the rest of the body. This method of therapy is beneficial in certain cases as an adjunct to surgical or radiation therapy. There is probably less disturbance to the host-tumor relationship when the drugs are confined to a limited area.

The radiotherapist will see at least 60 per cent of cancer patients at some time during their illness. He must be fully cognizant of the value, toxicity, complications and have a good working knowledge of the chemotherapeutic drugs. As an active participant in the treatment of cancer, he must keep an open mind and participate in every way that he can.

Much remains to be learned about the comparative effects of the chemotherapeutic agents used alone and when combined with radiation therapy. It is also necessary to know whether the combined effect is additive or synergistic. When good results have been obtained either by perfusion or systemic administration in combination with radiation therapy, how long the periodic systemic chemotherapy must be continued must be determined. The duration of action of the various agents must also be known as well as their mechanism of action. Is the combined effect better when the chemotherapy is given before, during, or after radiation therapy? These are but a few of many questions to be answered.

At the present time, none of the known chemotherapeutic agents are curative for cancer. Constant strides are being made, however, and eventually certain drugs may be found effective for certain types of tumors used singly or in combination with other drugs, radiotherapy, or surgery.

THERAPEUTIC MODIFICATION OF THE RADIATION RESPONSE

Every possible attempt is being made to increase the effectiveness of radiotherapy in the treatment of cancer. One of the most recent stimulating studies has been that by Gray and his associates[13,14,15] to further emphasize the basis that the irradiation of cancer patients under increased oxygen tension and increased atmospheric pressure will increase the radiosensitivity of poorly vascularized tumor tissue, thereby probably making the radiotherapy more effective.

Scott[27] found that the administration of oxygen, even at 1 atmosphere pressure, could definitely increase the regression of a tumor when irradiated. He also found that the regression produced by 1,000 r given in animal experimentation while the animal was breathing oxygen was essentially the same as from a dose of between 1,500 and 2,000 r given while the animal was breathing air.

Churchill-Davidson *et al.*[5,6] began a clinical trial in 1954 of using oxygenation in radiotherapy. Patients were chosen who had little, if any, chance of cure by conventional radiotherapy.

For the clinical trial the tumors in patients were irradiated while they were breathing oxygen at 3 and later at 4 atmospheres of absolute pressure. To prevent convulsions from the central nervous system disturbance by the oxygen, the patients were given barbiturates and chlorpromazine and a general anesthetic and an endotracheal tube inserted. Because of the increased barometric pressure and the possibility of rupture of the tympanic membranes, bilateral myringotomies were done and small polyethylene tubes left in place until the treatment was completed. The patient was placed in the pressure chamber and 15 minutes was allowed for changing the pressure. After the irradiation the patient was slowly decompressed.

By May, 1960,[5] 43 patients had been treated with conventional roentgen therapy (half value layer of 1.7 mm. copper). They were given a minimum tumor dose of 2,000 r in 2 fractions one week apart while breathing oxygen at an absolute pressure of 3 atmospheres. Forty-nine patients were treated with cobalt 60 while breathing oxygen at an absolute pressure of 4 atmospheres. The total tumor dose varied from 2,750 rads to 4,500 rads given in from 14 to 19 days. Eighty-nine of the 92 patients were studied and 18 or 20 per cent were found to be alive with no evidence of tumor growth for periods up to $4\frac{1}{2}$ years. They are sufficiently encouraged by the results to continue the study and they believe that the radiosensitivity of certain human cancers can be increased if the patient breathes oxygen at the time of irradiation.

There has been no randomized control series and this makes it difficult to evaluate the results. It may prove to be a problem to get a uniform distribution of oxygen throughout the tumor. If this is not done, then surviving tumor cells may be able to reproduce. In other words, if areas of anoxia persist during the irradiation, some of the tumor cells may not be affected by the irradiation. Du Sault *et al.*[8] have pointed out the possibility also that untreated metastatic lesions may be stimulated by the increased oxygen tension. They found in irradiating spontaneous mammary adenocarcinoma in C3H mice that the results are better if the mice breathe 95 per cent oxygen and 5 per cent carbon dioxide during treatment.

Gray[16] has stated that oxygen is of great interest to the radiotherapist because (1) oxygen is a normal physiologic variable; (2) oxygen affects radiosensitivity to a greater extent than any other agent tested to date; (3) hypoxic or anoxic foci militate against the curability of some tumors; and (4) oxygen can be controlled in experiments in man as well as in animals.

Other agents have been used to attempt to increase the radiosensitivity of tumor cells, such as, fluorescein, hydrogen peroxide (H_2O_2), glucose, insulin, and synkovite, but the results have not been too encouraging or consistent.

RADIOPROTECTIVE AGENTS

Studies are being made to find radioprotective and recovery promoting agents to increase the radiation tolerance of the host. Such agents as S, 2-aminoethylisothourea dihydrobromide (AET), mercaptoethylguamdine (MEG), cysteamine, and other compounds have been found to be effective in varying degrees in animals in providing radioprotection.

Research to find nontoxic effective radioprotective agents for man is particularly important since we are living in an unpredictable nuclear age. The radioprotective agents probably act on the basis of the production of anoxia in tissues and/or interference with the cellular metabolism and radiosensitivity and therefore would probably make tumor cells as well as normal cells less radiosensitive.

The necessity for continuing investigations in an attempt to find chemicals which will provide radioprotection from whole body irradiation in this changing world is obvious.

BONE MARROW REPLACEMENT

The radiosensitivity of the bone marrow is the limiting factor of the amount of irradiation which can be tolerated when the whole body or a major portion of the body is irradiated. It is probably much more difficult to attempt to restore injured cells to their normal function by biochemical means than it is to replace the damaged tissues. There is more interest in the concept that the damaged tissues have to be replaced at this time.

Following chemotherapy and total body irradiation the bone marrow is promptly affected to varying degrees depending upon the dose of irradiation. The granulocytes and platelets which have a normal span of only a few days must be continually replaced to help prevent infection and hemorrhage. The lymphocytes are extremely radiosensitive.

If the individual has not received a lethal dose of irradiation, antibiotics and blood transfusions may sustain his life until his own bone marrow is able to replace the platelets and other cells in the peripheral blood. If the bone marrow is severely damaged, anemia may occur which will persist until normal bone marrow function is restored.

The transplantation of foreign bone marrow and of other organs is possible if the immunity system of the individual has been sufficiently damaged or depressed. It is difficult to determine when the immunity system is depressed to its greatest extent, also just when is the optimum time to give the bone marrow transfusion.

It must be remembered that if the central nervous system or gastrointestinal tract is damaged beyond repair, the irradiation effects will not be changed by bone marrow transfusions (Smith and Congdon[28]).

There is a renewed interest in the use of whole body irradiation in the treatment of certain malignancies which may or may not involve the patient's own bone marrow. In those patients where the bone marrow is normal, and to whom it is planned to give total body irradiation or radiation to large areas of the body, the patient's own marrow can be taken and stored and then used again.

It is possible by bone marrow transplantation to replace the destroyed cells by the intravenous injection of the patient's own marrow which has been stored at $-79°$ C. in 15 per cent glycerol.[23]

The three and one-half year experience of Kurnick[22] with stored autologous bone marrow which has been administered following severe leukopenia and thrombocytopenia induced by radiotherapy or chemotherapy has convinced him that this method provides successful replacement therapy and extends the range of permissible myelosuppressive therapy.

The routine storing of bone marrow in patients who are to receive extensive radiotherapy has encouraged Feder and Kurnick[10] to give more intensive radiotherapy to larger areas in a shorter period of time.

Also they have been more inclined to complete a course of radiotherapy despite leukopenia and thrombocytopenia. At the present time they plan to store autologous bone marrow in all patients with seminoma and then use it later if indicated.

Sprague[30] has removed patients' bone marrow and stored it prior to the administration of large doses of nitrogen mustard (0.8 mg./kg.) and later reinfused it intravenously into the patient. The results were not conclusive and he was of the opinion that more studies were necessary.

IMPROVEMENTS IN RADIOTHERAPY EQUIPMENT

Although supervoltage therapy equipment has been available for many years, it has only been during the past 10 years that a great deal of interest and wide usage has occurred.

Some of the higher energy units now available are the 1 and 2 mev. G.E. resonance transformer types, the 2 mev. Van de Graaff apparatus, cobalt 60 kilocurie units with energy equal to that of a 3 mev. roentgen ray therapy unit, betatrons in the range of 20–30 mev., one 70 mev. synchrotron, and the linear accelerators from 4 to 15 or more mev.

One of the major questions to be answered is whether the 5 year survival rates will be improved following the use of supervoltage equipment over that obtained by the use of conventional or 250 kv. therapy. I believe sufficient evidence is beginning to appear to indicate that for certain tumors there is definitely better control when the higher energies are used.

Fletcher and his associates[11,12] have shown that there is better control when supervoltage therapy is used for certain head and neck lesions and also for Stage III carcinoma of the cervix cases when compared with conventional therapy. He also found it possible to sterilize metastatic disease in pelvic lymph nodes by supervoltage irradiation.

The advantages of supervoltage therapy are: (1) skin sparing effect; (2) less differential of absorption between bone and the soft tissues; (3) improved depth dose; (4) less tissue volume irradiated; (5) less radiation sickness; and (6) ease of operation and no change of filters necessary. The patients tolerate the treatments satisfactorily; most patients receive all their treatments as out patients. Hair usually regrows in heavily irradiated areas, and the palliation obtained is excellent in many cases.

Other areas in which the use of the higher energies has proved to be of considerable help are in the treatment of bladder and lung cancer. Although the treatment of lung cancer has been discouraging, we have attempted to assess the difference between the effect of conventional roentgen therapy and that of cobalt 60 therapy. Considerably better palliation was obtained in the cobalt 60 treated group in that the patients felt better for longer periods of time than when treated with conventional roentgen therapy and there was better control of hemoptysis, superior vena caval syndrome symptoms, severe cough, pain and dyspnea. The patients tolerated the therapy much better, and there were no appreciable skin reactions even with tumor doses in excess of 6,000 r.

There is considerable confusion in the literature regarding the selection of patients with urinary bladder cancer for various types of treatment. Most of the patients have had many different types of surgical and fulguration procedures, and much time has elapsed before they are referred to the radiotherapist for curative or palliative radiotherapy. In the past, the end results of treatment for high grade and deeply penetrating lesions of the bladder by either surgical or radiotherapeutic measures have not been too encouraging.

With the advent of the usage of higher energies (one million or more electron volts), renewed interest for the treatment of bladder carcinoma by means of radiotherapy has been stimulated.

With conventional roentgen therapy, it has been difficult to give a higher tumor dose (5,500 r to 6,000 r) without producing

marked frequency, dysuria, contraction of the bladder and other undesirable side effects.

It is quite possible that supervoltage therapy, given before extensive surgical procedures and particularly multiple procedures have been carried out in the more advanced stages of bladder carcinoma, could be more productive than surgery.

Our experience has been gained from the treatment of 99 bladder carcinomas during the past 6 years. Cobalt 60 therapy has been used externally and at a distance of 75 cm. We have given 5,000 or more r tumor dose in approximately 4 weeks to all patients where a "cure" has been attempted and approximately 3,000 r to those where only palliation was indicated.[24]

We are of the opinion that the high-grade infiltrative carcinomas will be greatly improved, and a moderate number will be cured by supervoltage therapy. If the patients are referred before they have had multiple surgical procedures and while in good clinical condition, the end results will be improved. Wound healing is delayed in the bladder following radiotherapy. Supervoltage therapy has not been effective for the low grade noninfiltrating bladder tumors. Again, I wish to stress the necessity for teamwork between the urologist and the radiotherapist.

TOTAL BODY IRRADIATION

Some of the advantages of supervoltage therapy have stimulated greater interest in the use of total body irradiation in the treatment of advanced malignancies and for use in the suppression of the immunologic response especially when the transplantation of organs such as the kidney has been contemplated.

The use of supervoltage therapy makes it possible to give total body radiation with roentgen rays or gamma rays of excellent quality and more economically than formerly.

King[19] has given total body radiation in total doses varying from 225 r to 900 r. Three of his patients received autologous bone marrow transplants but it was not definitely determined whether this influenced their clinical response. He is of the opinion that total body radiation therapy (225 to 400 r) is relatively safe and reasonably effective in producing palliation for patients with advanced malignant disease with radiosensitive tumors.

Thomas *et al.*[31] have studied in detail the question of whole body irradiation in patients with leukemia. Their observations suggest that total body radiation of 900, 1,200, and 1,600 r is not adequate to cure leukemia in man.

They also stated that "The relapses observed in the patients with isogenic grafts argue against the possibility of securing remissions of useful duration by general exposure to radiation and the implantation of samples of autologous marrow that have been stored during a previous period of remission."

SUMMARY

The specialty of radiotherapy is undoubtedly an active dynamic one. In the past 10 years alone there have been many new trends some of which are as follows:

1. Improved training for radiotherapists with growing recognition of the need for radiotherapy centers.

2. Necessity for the adequate teaching of radiation physics and radiation biology to all radiology trainees and not just emphasizing the training only to potential radiotherapists.

3. Need for all radiologists to become more familiar with the health and genetic hazards of living in a nuclear age. With the special training radiologists have had, they should become leaders to the medical profession and to the community with regard to the nuclear aspects of disaster medicine.

4. Many new chemotherapeutic compounds have been developed, some of which show promise as agents to be combined with radiation therapy. The radiotherapist must keep abreast of this changing field because any agent which will potentiate or be additive to the radiation

therapy effect must be investigated to the fullest extent. The use of the chemotherapeutic agents under scientific conditions by careful investigators with adequate reporting of findings to the medical profession will prevent the widespread indiscriminate use of these drugs.

5. The clinical trials of treating far advanced cancer patients with higher pressure oxygen atmosphere by Churchill-Davidson and his associates have been most valuable and have stimulated much interest and investigations by others.

6. Supervoltage therapy equipment is being widely used with probably improved survival rates over conventional roentgen therapy in certain types of tumors and also as a means of obtaining effective palliation.

7. With the use of supervoltage equipment, renewed interest in total body irradiation, radiation biology, bone marrow transplants and in organ transplants has occurred.

If the next ten years are as productive as the past decade, then certainly we have much to hope for in the ceaseless struggle against cancer.

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EDITORIALS

THE FORTY-FIFTH ANNUAL MEETING OF THE AMERICAN RADIUM SOCIETY

DURING a period of a few years, four decades ago, the *Archives de l'Institut du Radium de l'Université de Paris et de la Fondation Curie, Radiophysiologie et Radiothérapie*, published fundamental radiological data which have been the basis for modern radiotherapy. Since the time that those data appeared, no revolution in understanding the mechanism of the action of radiation on biological material occurred until the last decade, when great advances have been made in knowledge relating to radiochemistry and cellular radiobiology.

At the same time Sir Ronald Fisher initiated a new era in the handling of data when he published *Statistical Methods for Research Workers* in 1925. Since then, statistical methods have revolutionized many fields of science. The methods have been widely applied in agriculture, industry and commerce, and in the biological sciences. After World War II, the application of these methods to clinical medicine made an impact which is being noted increasingly. Computers, with their almost limitless possibilities, make the complex calculations of radiotherapy and statistical analysis almost routine. In the near future, information retrieval may cause unforeseen changes in the thinking of physicians. Medicine has been evolving continually; however, now, it is in a period of greatly accelerated change.

The keynote of the program prepared by the Scientific Program Committee of the American Radium Society for the Forty-fifth Annual Meeting is to evaluate in depth, by means of a series of symposia, problems of current interest. The Chairmen of the various symposia, Dr. Franz J. Buschke, Dr. Milton Friedman, Dr. Henry S. Kaplan, Dr. William S. MacComb, and Dr. J. J. Nickson, have secured the cooperation of basic scientists and clinicians from England, Canada, and the United States. Each of the invited essayists is a recognized expert in his respective field. This wide recruiting of talents was made possible by a generous contribution from Mr. James J. Picker.

The subjects to be presented in the symposia are: the fundamentals of radiobiology, the use of preoperative irradiation as an adjuvant to surgical therapy, a comprehensive review of the management of metastatic neck lymph nodes in the squamous cell carcinomas of the head and neck, the concept of Class I lymphomas, and a review of various schemes of fractionation which recently have been tried.

Our distinguished foreign guests will include Dr. Francois Baclesse of Paris, one of the deans of world radiotherapy; Dr. John Boag, Ph.D., of the Medical Research Unit of Mt. Vernon Hospital, England; Dr. Margaret Snelling, Deputy Director of the Myerstein Institute of Radiotherapy at the Royal Marsden Hospital in London; Dr. E. K. Sambrook, Consultant Radiotherapist at the Swansea and West Wales Hospital, England. These distinguished guests will either participate in the symposia or present papers on subjects in which they have extensive experience.

Several Canadian colleagues, some as members, some as guests of our society, will participate in the symposia or deliver essays on subjects of their choice. Dr. Jean Bouchard, our First Vice President, will give a paper on brain tumors. The Princess Margaret Hospital of Toronto will be well represented by Dr. M. Vera Peters, of the radiotherapy staff, Dr. Robert A. Mustard,

attending surgeon, and James Till, Ph.D., of the research staff who will participate in various symposia.

Because of the attractive location of the meeting, the Executive Committee has decided that the Scientific Sessions will be held only during the mornings from 9:00 A.M. to 1:00 P.M., leaving the afternoons for excursions, social activities, and scientific visits for those who hunger for more knowledge. Included will be visits to the Donner Laboratories in Berkeley and to the Radiation Therapy Departments at the University of California and Stanford University. Transportation for these visits will be provided.

With his committee members, Dr. Jerome M. Vaeth, Chairman of the Local Arrangements Committee, has worked out the details for the Scientific Sessions and for an outstanding Social Program.

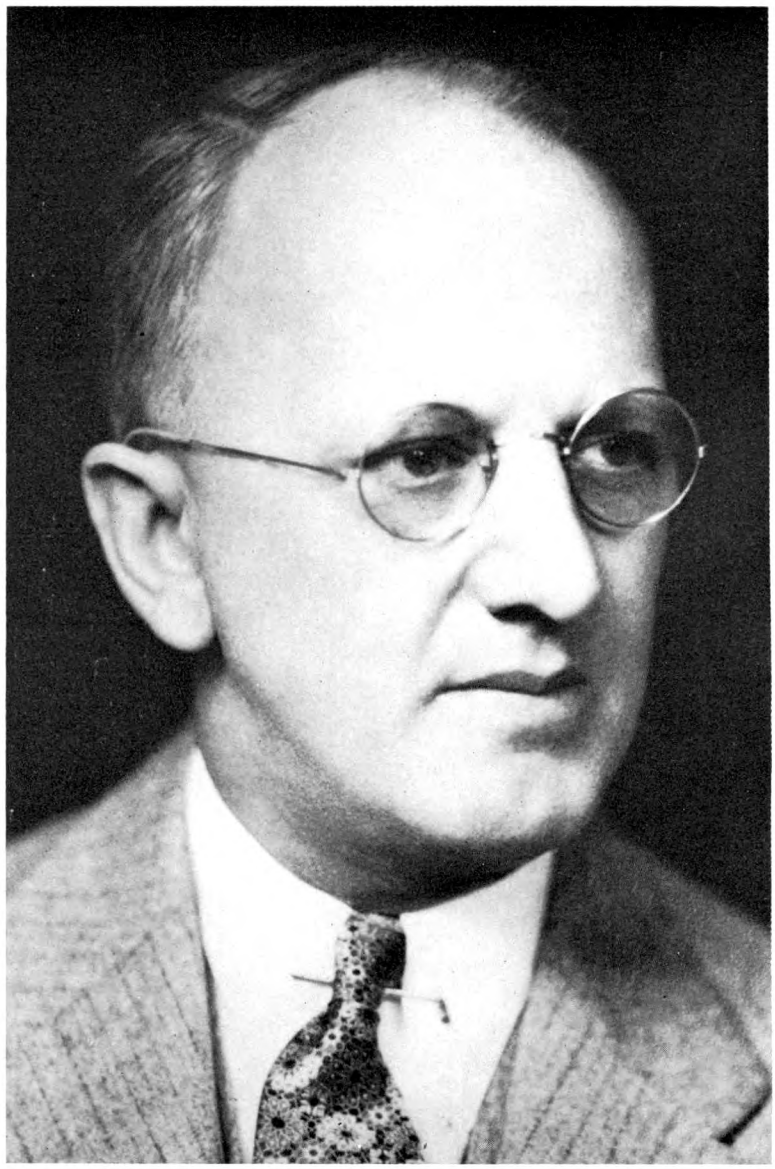
Thursday, April 4 at 8:00 o'clock, the evening of the last day of the meeting, Dr. Francois Baclesse will deliver the Low-Beer Memorial Lecture on the subject of breast cancer at the University of California Hospital in San Francisco. All who can should be prepared to stay a day longer for this memorable event.

Registration will begin on Sunday, March 31, from 12:00 noon until 6:00 P.M. It is urged that those who arrive on that day register in order that the scientific programs can start promptly at 9:00 A.M. on Monday. Those who enter their registrations early enough will be able to obtain rooms in the Mark Hopkins Hotel. However, for those who cannot secure a room there, the Fairmont Hotel, which is across the street, has reserved blocks of rooms for our members and guests.

The officers of the American Radium Society cordially invite you to attend the Forty-fifth Annual Meeting in San Francisco.

Gilbert H. Fletcher, M.D.,
President American Radium Society

The University of Texas M. D. Anderson
Hospital and Tumor Institute
Houston, Texas



DR. GERALD D. BLISS
1883-1962

DR. GERALD D. BLISS of 3409 Oak Lane, prominent Altoona physician and a pioneer in the use of the roentgen ray in Blair County, died on October 15, 1962 in the Altoona Hospital after a brief illness.

Dr. Bliss was born in Amherst, Nova Scotia, September 30, 1883, the son of Dr. Gerald C. W. and Elizabeth (Botsford) Bliss. He was educated in the local schools of Amherst and then after a few years' employment with a telephone company in the New England states he entered Jefferson Medical School, Philadelphia, Pennsylvania, graduating in 1907.

He came to Altoona December 12, 1907 to be an intern at the Altoona Hospital until July 1, 1908, after which he opened an office for the practice of medicine. He became interested in x ray work during his internship, limited his practice to the x ray and radium in 1914 and became the first Chief of Radiology at the Altoona Hospital, which position he held until January, 1950 when he retired to the emeritus staff. He then became Chief of Radiology at Altoona Veterans Hospital, October 10, 1950 until January, 1953. From 1915 until he died, he maintained his private office in addition to his hospital associations.

Dr. Bliss was a Diplomate of the American Board of Radiology, a Fellow of the American College of Radiology, member of the American Roentgen Ray Society, member of the Radiological Society of North America, Blair County Medical Society, Pennsylvania Medical Society and the American Medical Association. He was one of the founders and the first President of the Pennsylvania Radiological Society in 1916. He also served the latter organization as editor of its *Bulletin* from 1917 to 1920 and 1922 to 1934. He was a former President of the Blair County Medical Society and was Secretary-Treasurer of the Altoona Hospital Medical Staff for many years. In recent years he served the Blair County Chapter of the American Red Cross as attending physician at the various local blood donation centers.

Surviving are his wife, Mrs. Geraldine (Chapman) Bliss; two step-daughters, Mrs. Ruth Creighton of Dartmouth, Nova Scotia and Mrs. Beatrice Capreol of Toronto, Ontario; three brothers and two sisters, Blair B. Bliss of Vernon, British Columbia, Denison D. Bliss of Hamilton, Ontario, J. Donald Bliss of Victoria, British Columbia, Mrs. Madeleine Scovil of Amherst, Nova Scotia, and Mrs. Gwendolyn Wood of Vancouver, British Columbia. Also surviving is an aunt, Mrs. Hugh Hooper of Hudson Falls, N. Y.

Dr. Bliss was a member of the Masonic fraternity and of the Holy Trinity Episcopal Church of Hollidaysburg.

Marlyn W. Miller, M.D.

THE AMERICAN RADIUM SOCIETY

PROGRAM

The following is the program arranged by the Scientific Program Committee for the Forty-fifth Annual Meeting of the American Radium Society to be held at the Mark Hopkins Hotel, San Francisco, California, April 1–4, 1963.

Sunday, March 31, 1963

9:00 A.M.–4:00 P.M.
Executive Committee Meeting.

12:00 Noon–6:00 P.M.
Registration.

8:00 P.M.–9:30 P.M.
Tour of San Francisco.

Monday, April 1, 1963

8:00 A.M.
First Executive Session—for All Members.

9:00 A.M. Registration—onward.

Opening Ceremonies and Welcome Address.
Jerome M. Vaeth, M.D., Chairman, Committee of Arrangements.
University of California Hospitals, San Francisco, California.
Gilbert H. Fletcher, M.D., President, American Radium Society.
The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

FIRST SCIENTIFIC SESSION
Justin J. Stein, M.D., Chairman.
U.C.L.A. School of Medicine, Los Angeles, California.

9:15 A.M.
The "Second Look" Lymphography. R. Perez-Tamayo, M.D., and John R. Thornbury, M.D.,* University of Colorado Medical Center, Denver, Colorado.

9:30 A.M.
A Treatment System Utilizing Co^{60} Radiography, Transverse Planigraphy and Coordinated Techniques. Fred W. George, CDR, MC USN,* U. S. Naval Hospital, San Diego, California.

9:45 A.M.
Combined Chemo and Radiation Therapy in Advanced Squamous Cell Carcinoma of the Head and Neck. Simon Kramer, M.D., Jefferson Medical Center, Philadelphia, Pennsylvania.

10:00 A.M.
Some First Remarks about Statistics and Cancer. Lincoln E. Moses, Ph.D.,* Stanford University, Stanford, California.

10:30 A.M.
Coffee Break.

10:45 A.M.

Symposium:
The Fundamentals of Radiobiology. Henry S. Kaplan, M.D., Chairman, Palo Alto, California.
Primary Processes in Radiation Chemistry. John Boag, Ph.D.,* Mount Vernon Hospital, Middlesex, England.
Radiation Biochemistry. Henry S. Kaplan, M.D., Stanford University School of Medicine, Palo Alto, California.
Quantitative Aspects of Radiation Lethality at the Cellular Level. James Till, Ph.D.,* Ontario Cancer Institute, Toronto, Canada.
Quantitative Aspects of Radiation Effect at the Tissue and Tumor Level. Harvey M. Patt, Ph.D.,* Argonne National Laboratory, Argonne, Illinois.

1:00 P.M.
Adjournment of First Scientific Session.

6:00 P.M.
Social hour—followed by dinner—St. Francis Yacht Club.

Tuesday, April 2, 1963

8:00 A.M.
Second Executive Session.

9:00 A.M.
SECOND SCIENTIFIC SESSION
Jean Bouchard, M.D., Chairman.
Royal Victoria Hospital, Montreal, Canada.

Symposium:
Lymphomas. James J. Nickson, M.D., Chairman, Memorial Hospital for Cancer and Allied Diseases, New York City.
Role of Chemotherapy in the Management of Class 1 Hodgkin's Disease. David Karnofsky, M.D.,* Memorial Hospital for Cancer and Allied Diseases, New York City.
Natural History of Class 1 Lymphomas. Alan C. Scheer, M.D.,* Memorial Hospital for Cancer and Allied Diseases, New York City.
Policy of Treatment of Class 1 Lymphomas.

* By invitation.

* By invitation.

M. Vera Peters, M.D., Ontario Cancer Institute, Toronto, Canada.

Histopathological Considerations of Potential Prognostic Significance. Robert J. Lukes, M.D.,* Armed Forces Institute of Pathology, Washington, D. C.

10:30 A.M.
Coffee Break.

10:45 A.M.
The Influence of Time-spacing of Fractions on the Response to Radiation. Lucille A. Du Sault, Henry Ford Hospital, Detroit, Michigan.

11:00 A.M.
Breast Carcinoma—260 Cases Treated Postoperatively with 2 Mev X-ray. Magnus I. Smedal, M.D., Ferdinand A. Salzman, M.D.,* David O. Johnston, M.D.,* John R. Hewetson, M.D.,* John G. Trump, Sc.D., and Kenneth A. Wright, M.S.,* Lahey Clinic, Boston, Massachusetts.

11:15 A.M.
Results of Ultra-Fractionation Radiotherapy in Breast Carcinoma. Maureen Archambault, M.D.,* Melvin L. Griem, M.D.,* and David J. Lochman, M.D., University of Chicago Clinics and Columbus Hospital, Chicago, Illinois.

11:30 A.M.
Description of a Method and Results of Treatment of Breast Carcinoma with Cobalt 60 Teletherapy. George P. Koeck, M.D., Lillian E. Jacobson, M.A., and W. R. Hillsinger, B.S.,* Presbyterian Hospital Unit, United Hospitals of Newark, New Jersey.

11:45 A.M.
Question Period—opened by Jerome A. Urban, M.D., Memorial Hospital for Cancer and Allied Diseases, New York City.

12:00 NOON

THE JANEWAY LECTURE

Long Term Observations in Endometrial Cancer. A. N. Arneson, M.D., Washington University School of Medicine, St. Louis, Missouri.

Introduced by Lloyd F. Craver, M.D., New York City.

1:00 P.M.
Adjournment of Second Scientific Session.

2:00 P.M.–4:00 P.M.
Dry Clinic—Department of Radiology, University of California Hospitals, San Francisco, California.

5:30 P.M.
Tour of San Francisco Harbor.

* By invitation.

Wednesday, April 3, 1963

8:00 A.M.
Third Executive Session.

9:00 A.M.

THIRD SCIENTIFIC SESSION

Jerome A. Urban, M.D., Chairman.
Memorial Hospital for Cancer and Allied Diseases, New York City.

Symposium:

Protraction and Fractionation. Franz J. Buschke, M.D., Chairman, University of California Hospitals, San Francisco, California.

Ultra-Protraction. Dr. F. Baclesse, The American Hospital of Paris, France.

Split Course Technique. Dr. D. K. Sambrook,* Swansea and West Wales Hospital, England.

Periodic Fractionation. Charles Botstein, M.D., Montefiore Hospital, New York City.

Massive Single Dose Technique. Harold L. Atkins, M.D.,* Presbyterian Hospital, New York City.

10:30 A.M.
Coffee Break.

10:45 A.M.

Symposium:

Pre-operative Irradiation. Milton Friedman, M.D., Chairman, Hospital for Bone & Joint Diseases, New York City.

Endometrial Carcinoma. Isadore Lampe, M.D., Ph.D., University Hospital, Ann Arbor, Michigan.

Breast. Edgar C. White, M.D.,* The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

Bladder. Willett Whitmore, M.D.,* Memorial Hospital for Cancer and Allied Diseases, New York City.

Lung. Fernando G. Bloedorn, M.D., University of Maryland Hospitals, Baltimore, Maryland.

Head and Neck. Sidney Silverstone, M.D., and Joseph Goldman, M.D.,* Mount Sinai Hospital, New York City.

1:00 P.M.
Adjournment of Third Scientific Session.

2:00 P.M.–4:30 P.M.
Tour—Stanford Medical Center, Palo Alto, California; Donner Laboratory, Radiation Center, Berkeley, California.

7:00 P.M.
Social Hour—Mark Hopkins Hotel.

8:00 P.M.
Annual Banquet—Mark Hopkins Hotel.

* By invitation.

Thursday, April 4, 1963

8:00 A.M.
Fourth Executive Session.

9:00 A.M.
FOURTH SCIENTIFIC SESSION
Grant Beckstrand, M.D., Chairman.
Long Beach, California.

The Place of Radiotherapy in the Treatment of Malignant Tumors of Base of Tongue. Vera M. Dalley, M.D.,* The Royal Marsden Hospital, London, England.

9:20 A.M.
Histology, Natural History and Results of Treatment of Salivary Gland Tumors. Margaret D. Snelling, F.R.C.S., F.F.R.,* Myerstein Institute of Radiotherapy, The Middlesex Hospital, London, England.

9:40 A.M.
Treatment of Tumors of the Central Nervous System with Surgery Followed by Irradiation or Irradiation Alone. Jean Bouchard, M.D., D.M.R.E. (Cantab.), F.A.C.R., Royal Victoria Hospital, Montreal, Canada.

10:00 A.M.
Intracranial Ependymomas. A Study of Survival with Surgery and Radiation Therapy. Irwin I. Kricheff, M.D.,* Melvin Becker, M.D.,* Stewart Schneck, M.D.,* and Juan M. Taveras, M.D.,* Neurological Institute and New York University, New York City.

* By invitation.

10:20 A.M.
Question Period.

10:30 A.M.
Coffee Break.

10:45 A.M.

Symposium:
Management and End Results in the Treatment of Metastatic Cervical Lymph Nodes. William S. MacComb, M.D., Chairman, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas.
Oral Cavity. Robert A. Mustard, M.D.,* Ontario Cancer Institute, Toronto, Canada.
Oropharynx. Richard H. Jesse, M.D., The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas.
Hypopharynx (Including Pyriform Sinus). Lewis W. Guiss, M.D., Los Angeles, California.
Intrinsic and Extrinsic Larynx (Supraglottic, Glottic, and Subglottic Cancers). John V. Blady, M.D., Philadelphia, Pennsylvania.

12:45 P.M.
Final Executive Session for All Members and Installation of New Officers.

Adjournment of the Forty-fifth Annual Meeting of the American Radium Society.

* By invitation.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

The Year Book of Radiology (1961–1962 Year Book Series). Radiologic Diagnosis. Edited by John Floyd Holt, M.D., Professor, Department of Radiology, University of Michigan; and Walter M. Whitehouse, M.D., Associate Professor, Department of Radiology, University of Michigan, Ann Arbor, Mich. Radiation Therapy. Edited by Harold W. Jacox, M.D., Professor of Radiology, College of Physicians and Surgeons, Columbia University; Chief, Radiation Therapy Division, Radiologic Service, Presbyterian Hospital, New York City; and Morton M. Kligerman, M.D., Professor of Radiology and Chairman of the Department of Radiology, Yale University School of Medicine; Director of Radiology, Grace-New Haven Community Hospital. Cloth. Price, $11.00. Pp. 433, with 344 illustrations. Year Book Medical Publishers, 200 East Illinois Street, Chicago, Ill., 1962.

The field of radiology is constantly advancing with an increasing rapidity. It is impossible for the occupied radiologist to read all of the necessary and important literature required to keep him abreast of the advances and new discoveries in his specialty. The 1961–1962 Year Book Series again fulfills this requirement by concisely reviewing, condensing, and editing material from the world medical literature pertinent to technical advances, clinical observations, and theoretical innovations in roentgen diagnosis and therapy.

New applications of image intensification supplemented with television and video tape offer exciting possibilities in the new era of diagnostic roentgenology through which we are now passing. Cerebral and coronary arteriography, lymphadenography, and isotope encephalography and radioautography are but a few of the numerous articles on special subjects which have been abstracted, some appearing in foreign journals. Continued refinement of roentgen observation in classic diseases is also evident. Bone changes in anemias, further evaluation of chronic pulmonary diseases, retroperitoneal fibrosis, medullary sponge kidneys, and esophageal physiologic studies are but a sampling of subjects reviewed.

Many excellent articles on radiation and isotope therapy were reviewed with appropriate editorial comment. Investigations of various compounds in altering radiation sensitivity and reducing lethal effects are described. Outstanding papers at the American Radium Society Meeting in May, 1961 were reviewed including the important one of Sigvard Kaae of Copenhagen, which evaluated relative results of surgery and radiation therapy in breast carcinoma.

This book should be required reading for all radiologists as well as students in this field.

Arch H. Hall, M.D.

Atlas of Tumor Pathology. Section II-Fasc. 4. Tumors of Bone and Cartilage. By Lauren V. Ackerman, M.D., Professor of Surgical Pathology and Pathology, Washington University School of Medicine, St. Louis, Mo.; Surgical Pathologist, Barnes Hospital and Affiliated Hospitals, St. Louis, Mo.; Consultant to the Armed Forces Institute of Pathology, Washington, D. C.; and Harlan J. Spjut, M.D., Associate Professor of Surgical Pathology, Washington University School of Medicine, St. Louis, Mo.; Associate Surgical Pathologist, Barnes Hospital and Affiliated Hospitals, St. Louis, Missouri. Paper. Price, $3.00. Pp. 347, with 362 illustrations. American Registry of Pathology, Armed Forces Institute of Pathology, Washington 25, D. C., 1962.

Perhaps the best way to review this fascicle of the Atlas of Tumor Pathology would be to use current consumer terminology and list it as a "best buy." Although in recent years several monographs on bone tumors have appeared, some in the form of textbooks and some as atlases, the present volume is commended as it combines many of the best features of these prior publications. As usual in these fascicles, the quality of the photographs is superb and surpasses all others available. The accompanying text is adequate without being verbose. When knowledge of a subject is lacking, the

authors do not hesitate to say so, but ample references are provided for those interested in a more detailed discussion. A minor annoyance in this respect is the page arrangement which splits consecutive pages of references, hiding them among the illustrations. The value of correlating clinical, radiologic and pathologic findings in arriving at a diagnosis in bone lesions is stressed, as is the importance of tissue examination concurrently with surgery in planning definitive therapy. Even if the pathologist is unable to process the tissue because of its bony content, or is unable to reach a diagnosis, the examination of the fresh tissue at least ensures that an adequate sample of the lesion has been obtained.

A valuable chapter is devoted to radiation-induced sarcomas of bone, some of which have followed roentgen therapy of benign lesions. Issue might be taken with the statement that osteoblasts are never seen in fibrous dysplasia of bone but criticism such as this merely emphasizes the over-all excellence of the volume.

In summary, the library of a practicing orthopedic surgeon, radiologist or pathologist, or a resident in one of these fields will be incomplete without this fascicle.

A. R. W. CLIMIE, M.D.

BOOKS RECEIVED

EINFÜHRUNG IN DIE MESSTECHNIK DER KERNSTRAHLUNG UND DIE ANWENDUNG DER RADIOISOTOPE. By Prof. Dr. phil. Heinrich Fassbender, Em. ord. Professor der Technischen Universität Berlin, Erlangen, Berlin; and H. Breiheller, C. W. Fassbender, H. Fassbender, W. Klein, H. Liesegang, H. Munzel, and K. H. Waechter. Cloth. Price, DM 49.50. Pp. 420 with 240 illustrations. Georg Thieme Verlag, Herdweg 63, Stuttgart N, Germany. In the USA and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y., 1962.

INTRAVENOUS CHOLANGIOGRAPHY. By Robert E. Wise, B.S., M.D., F.A.C.R., Radiologist, The Lahey Clinic and New England Baptist Hospital, Boston, Massachusetts. Cloth. Price, $9.50. Pp. 139 with numerous illustrations. Charles C Thomas, Publisher, 301–327 East Lawrence Ave., Springfield, Ill., 1962.

THE THYROID. Second Edition. A Fundamental and Clinical Text, with Sixty-Five Contributors. Edited by Sidney C. Werner, M.D., Sc.D. (Med.). Cloth. Price, $24.00. Pp. 873 with numerous illustrations. Harper & Row, Publishers, Inc., 49 East Thirty-Third Street, New York 16, N. Y., 1962.

CHILDREN'S RADIOGRAPHIC TECHNIC. Second Edition. By Forrest E. Shurtleff, R.T., Chief Technician, Robert B. Brigham Hospital, Boston, Massachusetts; Formerly, Chief Technician, Children's Medical Center, Boston, Massachusetts. Cloth. Price, $4.50. Pp. 92 with numerous illustrations. Lea & Febiger, Washington Square, Philadelphia 6, Pa., 1962.

TODD-SANFORD CLINICAL DIAGNOSIS BY LABORATORY METHODS. Thirteenth Edition. Edited by Israel Davidsohn, M.D., F.A.C.P., Chairman, Department of Pathology, The Chicago Medical School, Director, Department of Pathology, Mount Sinai Hospital and Scientific Director, Mount Sinai Medical Research Foundation, Chicago; and Benjamin B. Wells, M.D., Ph.D., F.A.C.P., Dean, California College of Medicine, Los Angeles; Formerly Assistant Chief Medical Director for Research and Education in Medicine, The Veterans Administration, Washington, D. C. Cloth. Price, $16.50. Pp. 1020 with numerous illustrations. W. B. Saunders Company, Philadelphia, Pa., 1962.

MODERN RADIOLOGY IN HISTORICAL PERSPECTIVE. By Stephen B. Dewing, M.D., Director of Radiology, Hunterdon Medical Center, Flemington, New Jersey, Associate Clinical Professor of Radiology, New York University Post Graduate Medical School, New York City; with a foreword by Maxwell H. Poppel, Professor and Chairman, Department of Radiology, New York University Medical College. Cloth. Price, $5.75. Pp. 189. Charles C Thomas, Publisher, 301–327 East Lawrence Ave., Springfield, Ill., 1962.

EXAMINATION AND DIAGNOSIS OF THE SPINE AND EXTREMITIES. By Beckett Howorth, M.D., Med. Sc.D., Clinical Professor of Orthopedic Surgery, New York University Post Graduate Medical School, New York City, Lecturer in Orthopedics, Yale University School of Medicine, New Haven, Connecticut. Cloth. Price, $10.50. Pp. 178 with 180 illustrations. Charles C Thomas, Publisher, 301–327 East Lawrence Ave., Springfield, Ill., 1962.

SELECTED PAPERS FROM THE INSTITUTE OF CANCER RESEARCH: ROYAL CANCER HOSPITAL AND FROM THE ROYAL MARSDEN HOSPITAL, 1960. Published by order of the Committee of Management of the Institute and the Board of Governors of the Royal Marsden Hospital, London, England. Volume 15. Cloth. Pp. 1151 with numerous illustrations. Printed by Lund Humphries, London, England, 1962.

INTERNATIONAL DIRECTORY OF RADIOISOTOPES. Second Edition, Revised. International Atomic Energy Agency, Vienna, 1962. Cloth. Pp. 1181. Distributed by National Agency for International Publications, Inc., 801 Third Avenue, New York 22, N. Y., 1962.

REPORT OF THE UNITED NATIONS SCIENTIFIC COMMITTEE ON THE EFFECTS OF ATOMIC RADIATION. General Assembly. Official Records: Seventeenth Session. Supplement No. 16 (A/5216). Paper. Price, $5.00. Pp. 439. United Nations, New York, 1962.

NEWS ITEMS

THE ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

At the last Annual Meeting of the Rocky Mountain Radiological Society, the following new officers were elected for 1963: *President*, Dr. Vernon L. Bolton, Colorado Springs, Colorado; *President-Elect*, Dr. John F. Bacon, Ames, Iowa; *1st Vice-President*, Dr. Donald H. Breit, Sioux Falls, South Dakota; *2nd Vice-President*, Dr. Don L. Vickery, Pueblo, Colorado; *Secretary-Treasurer*, Dr. John H. Freed, Denver, Colorado; and *Historian*, Dr. H. Milton Berg, Bismarck, North Dakota.

The next Annual Meeting will be held in Denver at the Denver Hilton Hotel on August 22, 23 and 24, 1963.

EASTERN CONFERENCE OF RADIOLOGISTS

In the October, 1962 issue of the JOURNAL it was announced that the Eastern Conference of Radiologists is meeting in Philadelphia, Pennsylvania on April 4, 5 and 6, 1963.

Dr. Theodore A. Tristan has been appointed as the new Secretary of the Conference.

For further information relative to the Conference, please contact Dr. Theodore A. Tristan, Secretary, Hospital of the University of Pennsylvania, Philadelphia 4, Pennsylvania.

THE ASSOCIATION OF UNIVERSITY RADIOLOGISTS

Annual Memorial Medal Award Competition

An Annual Memorial Medal Award, in honor of deceased AUR members, is awarded to the resident in radiology writing the best original paper on some aspect of radiology during the period of competition. The paper must be the work of only one author, the resident. Manuscripts to be considered for the 1963 competition must be received by March 1, 1963. Inquiries should be addressed and papers submitted to the Secretary, John A. Campbell, M.D., Department of Radiology, Indiana University Medical Center, Indianapolis 7, Indiana.

The 1962 Memorial Medal Award was won by Sadek Hilal, M.D., University of Minnesota, for his paper, "Determination of the Blood Flow by a Radiographic Technique," presented at the recent meeting of the Association at Indiana University Medical Center, Indianapolis.

The 1963 annual meeting will be held at Yale University in New Haven, Connecticut, May 24 and 25.

POSTGRADUATE COURSE IN "ADVANCES IN ANGIOGRAPHY"

This postgraduate course arranged by the University of Miami School of Medicine and National Children's Cardiac Hospital is designed to acquaint radiologists, cardiologists, and physicians interested in angiography in the recent advances and newer developments of this growing field. The following aspects will be covered: (1) technical procedures; (2) coronary arteriography; (3) angiocardiography; (4) abdominal angiography; (5) splenoportography; (6) neuroangiography; (7) lymphangioadenography; (8) venography; and (9) peripheral arteriography.

Sessions will be held on Thursday, March 28; Friday, March 29; and Saturday, March 30, 8:30 A.M. to 4:00 P.M.; and Sunday, March 31, 9:00 A.M. to 12:00 NOON, 1963 at the Fontainebleau Hotel, Miami Beach, Florida.

A total of 39 papers and 7 General Discussions will be presented by an outstanding Faculty.

The Guest Faculty includes: Drs. Herbert L. Abrams, Charles T. Dotter, Benjamin Felson, Harry W. Fischer, Owings W. Kincaid, J. Stauffer Lehman, Russell H. Morgan, Donald L. McRae, Olle Olsson, Robert A. Schobinger, F. Mason Sones, Jr., Israel Steinberg and Juan M. Taveras.

The Local Faculty comprises: Drs.

Donald Altman, Robert J. Boucek, Agustin Castellanos, Sr., Francis N. Cooke, Robert F. Feltman, Francisco Hernandez, Allan A. Kaplan, William P. Murphy, Jr., Phillip Samet, Peritz Scheinberg, Leonard S. Sommer and Manuel Viamonte, Jr.

For further information please write to the Director: Raymond E. Parks, M.D., Professor and Chairman of Radiology, University of Miami School of Medicine, Jackson Memorial Hospital, Miami 36, Florida.

NEW OFFICERS OF THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

At the Forty-eighth Annual Meeting of the Radiological Society of North America held November 25–30, 1962, at the Palmer House, Chicago, Illinois, the following officers were elected: *President*—Ivan J. Miller, M. D., San Francisco, California; *President-Elect*—Robert P. Barden, M.D., Philadelphia, Pennsylvania; *First Vice President*—John R. Hodgson, M.D., Rochester, Minnesota: *Second Vice President*—Lawrence A. Davis, M.D., Louisville, Kentucky; *Third Vice President*—Lee B. Lusted, M.D., Portland, Oregon; *Secretary*—Maurice D. Frazer, M.D., Lincoln, Nebraska; *Treasurer*—Dwight V. Needham, M.D., Syracuse, New York; and *Historian*—Howard P. Doub, M.D., Detroit, Michigan. Dr. Robert D. Moreton, Fort Worth, Texas, is the new *Chairman of the Board of Directors*. The new member elected to the *Board of Directors* is Dr. Stanley M. Wyman of Cambridge, Massachusetts.

The Gold Medal of the Society was awarded to Dr. Arthur C. Singleton of Toronto, Ontario, Canada.

The Forty-ninth Annual Meeting will be held at the Palmer House, Chicago, Illinois, November 17–22, 1963.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Queen Elizabeth Hotel, Montreal, Que., Canada, Oct. 8–11, 1963.

American Radium Society
Secretary, Dr. Justin J. Stein U.C.L.A. Medical Center, Los Angeles 24, Calif. Annual meeting: Mark Hopkins Hotel, San Francisco, Calif., April 1–4, 1963.

Radiological Society of North America
Secretary, Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb.
Treasurer, Dwight Vincent Needham, 713 E. Genessee St., Syracuse, N. Y. Annual meeting: Palmer House, Chicago, Ill., Nov. 17–22, 1963.

American College of Radiology
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting: Drake Hotel, Chicago, Ill., Feb. 6–9, 1963.

Section on Radiology, American Medical Association
Secretary, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eighth Ave., Spokane 4, Wash. Annual meeting: Atlantic City, N. J., June 16–20, 1963.

American Board of Radiology
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn. The Spring 1963 examination will be held at the Sheraton Hotel, Philadelphia, Pennsylvania, June 3–7, inclusive. Deadline for filing applications was December 31, 1962. There will be a Special Examination in Nuclear Medicine for diplomates in Radiology or Therapeutic Radiology if sufficient applications are received. The Fall 1963 examination will be held at the Terrace Hilton Hotel, Cincinnati, Ohio, December 2–6, inclusive. Deadline for filing applications is June 30, 1963.

American Association of Physicists in Medicine
Secretary-Treasurer, Charles S. Simons, University of Michigan Hospital, Ann Arbor, Mich. Annual meeting to be announced.

Eleventh International Congress of Radiology
Secretary-General, Professor Dr. Med. Ardunio Ratti, via Moscova, 44-1, Milan, Italy. Address inquiries to Professor Dr. Med. Luigi Turano, President-Elect, Istituto di Radiologia, Università di Roma, Rome, Italy. Meeting: September, 1965.

Eighth Inter-American Congress of Radiology
Counselor for the United States, Dr. Philip J. Hodes, Jefferson Medical College Hospital, 11th and Walnut Streets, Philadelphia 7, Pennsylvania.
Secretary, Dr. Mario Gaitan-Yanguas, Bogotá, Colombia. Meeting to be announced.

Alabama Radiological Society
Secretary, Dr. Walter Brower, Birmingham, Ala. Meets time and place Alabama State Medical Association.

American Nuclear Society
Treasurer, Raymond Maxson, 86 E. Randolph St., Chicago, Ill.

Arizona Radiological Society
Secretary, Dr. E. Lawrence Ganter, 1820 E. Polk St., Phoenix 34, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Radiological Society
Secretary, Dr. Charles W. Anderson, 1108½ Poplar, Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

Association of University Radiologists
Secretary, Dr. John A. Campbell, Indiana University Medical Center, Indianapolis, Ind. Annual meeting: Yale University Medical Center, New Haven, Conn., May 24–25, 1963.

Atlanta Radiological Society
Secretary, Dr. Wilson T. Edenfield, 35 Linden Ave., N.E., Atlanta 8, Ga. Meets monthly, except during three summer months, on second Friday evening.

Blockley Radiological Society
Secretary, Dr. Bernard J. Ostrum, 2412 North 52nd St., Philadelphia, Pa.

Brooklyn Radiological Society
Secretary, Dr. Peter J. Lampros, Brooklyn, N. Y. Meets first Thursday of each month October through May.

Buffalo Radiological Society
Secretary, Dr. Edward A. Dunlap, Jr., 35 Danbury Lane, Kenmore 17, N. Y. Meets second Monday evening each month, October to May inclusive.

California Radiological Society
Secretary, Dr. L. Henry Garland, Suite 1739, 450 Sutter St., San Francisco, Cal. Meets annually during meeting of California Medical Association.

Central New York Radiological Society
Secretary, Dr. Edward W. Carsky, Crouse-Irving Hospital, 820 S. Crouse Ave., Syracuse, N. Y. Meets first Monday each month October through May.

Central Ohio Radiological Society
Secretary, Dr. Dana R. Schmidt, 1500 West Third Ave., Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

Central Society of Nuclear Medicine
Secretary, Dr. Robert S. Landauer, Radiation Center Bldg., 1903 West Harrison St., Chicago 12, Ill.

Chicago Roentgen Society
Secretary, Dr. Abram Cannon, Chicago Wesley Memorial Hospital, 250 E. Superior St., Chicago 11, Ill. Meets second Thursday of each month, October to April except December at the Pick-Congress Hotel at 8:00 P.M.

Cleveland Radiological Society
Secretary, Dr. Ward D. Heinrich, Huron Road Hospital, Cleveland 12, Ohio. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and April.

Colorado Radiological Society
Secretary, Dr. Seward Imes, 1845 High St., Denver, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

Connecticut Valley Radiologic Society
Secretary, Dr. James L. Krieger, 85 Jefferson St., Hartford 6, Conn. Meets first Friday in February and April.

Dallas-Fort Worth Radiological Society
Secretary, Dr. Robert D. Moreton, 816 Medical Arts Bldg., Fort Worth, Tex. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. Arch H. Hall, Harper Hospital, Detroit 1, Mich. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

East Bay Roentgen Society
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9,

* Secretaries of societies are requested to send timely information promptly to the Editor.

Calif. Meets first Thursday each month at Peralta Hospital, Oakland, Calif.

EAST TENNESSEE RADIOLOGICAL SOCIETY
Secretary, Dr. J. Marsh Frere, Jr., 205 Medical Arts Bldg., Knoxville, Tenn. Meets in January and September.

EASTERN CONFERENCE OF RADIOLOGISTS
Secretary, Arrangements Committee, Dr. Theodore A. Tristan, 3400 Spruce St., Philadelphia 4, Pa. Annual Meeting: April 4–6, 1963, Philadelphia, Pa.

EASTERN RADIOLOGICAL SOCIETY
Secretary, Dr. James F. Martin, North Carolina Baptist Hospital, Winston-Salem, N. C.

FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. Marvin V. McClow, St. Vincent's Hospital, Barrs and St. Johns Ave., Jacksonville 4, Fla. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

FLORIDA WEST COAST RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Joseph C. Rush, 1800 Druid Rd., Clearwater, Fla.

GEORGIA RADIOLOGICAL SOCIETY
Secretary, Dr. George W. Brown, Griffin, Ga. Meets in spring and fall with Annual State Society Meeting.

GREATER MIAMI RADIOLOGICAL SOCIETY
Secretary, Dr. T. Hunter Pryor, Jackson Memorial Hospital, Miami 36, Fla. Meets monthly, third Wednesday, at 8:00 P.M. at Jackson Memorial Hospital, Miami, Fla.

GREATER ST. LOUIS SOCIETY OF RADIOLOGISTS
Secretary, Dr. Harry I. Berland, St. Louis, Mo.

HOUSTON RADIOLOGICAL SOCIETY
Secretary, Dr. W. E. Kirkpatrick, 2708 Weslayan, Houston 27, Tex. Meets last Monday each month in fall, winter and spring, Seminar Room, Doctors' Club of Houston.

IDAHO STATE RADIOLOGICAL SOCIETY
Secretary, Dr. George H. Harris, Bannock Memorial Hospital, Pocatello, Idaho. Meets in the spring and fall.

ILLINOIS RADIOLOGICAL SOCIETY
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in the spring and fall.

INDIANA ROENTGEN SOCIETY, INC.
Secretary, Dr. Richard A. Silver, 712 Hume Mansur Bldg., Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

IOWA RADIOLOGICAL SOCIETY
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

KANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. Roger K. Wallace, Riley County Hospital, Manhattan, Kan. Meets in spring with State Medical Society and in winter on call.

KENTUCKY RADIOLOGICAL SOCIETY
Secretary, Dr. Lawrence A. Davis, 226 East Chestnut St., Louisville, Ky. Meets monthly on second Friday at Sheraton Hotel, Louisville.

KINGS COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. Abraham Berens, 1917 Bedford Ave., Brooklyn 25, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

KNOXVILLE RADIOLOGICAL SOCIETY
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

LOS ANGELES RADIOLOGICAL SOCIETY
Secretary, Dr. Chester P. Bonoff, 1930 Wilshire Blvd., Los Angeles 57, Cal. Meets second Wednesday of month in September, November, January, March and June at Los Angeles County Medical Association Building, Los Angeles.

MAINE RADIOLOGICAL SOCIETY
Secretary, Dr. Charles W. Capron, Maine Medical Center, Portland, Me. Meets in June, September, December and April.

MARYLAND RADIOLOGICAL SOCIETY
Secretary, Dr. James A. Lyon, Jr., 7918 Springway Rd., Ruxton 4, Maryland.

MEMPHIS ROENTGEN SOCIETY
Secretary, Dr. Irving K. Ettman, Kennedy V.A. Hospital, Department of Radiology, Memphis 15, Tenn. Meets first Monday of each month at John Gaston Hospital.

MIAMI VALLEY RADIOLOGICAL SOCIETY
Secretary, Dr. William D. Roberts, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

MID-HUDSON RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph Sorrentino, St. Francis Hospital, Poughkeepsie, N. Y. Meets 8:30 P.M., fourth Wednesday of each month September to May.

MILWAUKEE ROENTGEN RAY SOCIETY
Secretary, Dr. Abraham Marck, Mayfair Professional Bldg., Milwaukee 13, Wis. Meets monthly on fourth Monday, October through May, at University Club.

MINNESOTA RADIOLOGICAL SOCIETY
Secretary, Dr. Frank J. Anderson, 810 E. 27th St., Minneapolis 7, Minn. Meets three times annually, in fall, winter and spring.

MISSISSIPPI RADIOLOGICAL SOCIETY
Secretary, Dr. Jack K. Goodrich, University Medical Center, Jackson, Miss. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.

MONTANA RADIOLOGICAL SOCIETY
Secretary, Dr. John M. Fritts, 1224 S. Higgins Ave., Missoula, Montana. Meets at least once a year.

NASSAU RADIOLOGICAL SOCIETY
Secretary, Dr. Herbert Kantor, 71 S. Oyster Bay Rd., Syosset, N. Y. Meets second Tuesday of the month in February, April, June, October and December.

NEBRASKA STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Richard Bunting, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Neb. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

NEVADA RADIOLOGICAL SOCIETY
Secretary, Dr. William G. Arbonies, Department of Radiology, St. Mary's Hospital, Reno, Nev.

NEW ENGLAND ROENTGEN RAY SOCIETY
Secretary, Dr. Robert E. Wise, 605 Commonwealth Ave., Boston 15, Mass. Meets third Friday of each month, October through April, at The Longwood Towers, Brookline, Mass. at 4:30 P.M.

NEW HAMPSHIRE ROENTGEN RAY SOCIETY
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

NEW YORK ROENTGEN SOCIETY
Secretary, Dr. James J. Nickson, Memorial Hospital, New York, N. Y. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M.

NORTH CAROLINA RADIOLOGICAL SOCIETY
Secretary, Dr. A. B. Croom, 624 Quaker Lane, High Point, N. C. Meets in the spring and fall each year.

NORTH DAKOTA RADIOLOGICAL SOCIETY
Secretary, Dr. John Jestadt, Depuy-Sorkness Clinic, Jamestown, N. D. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

NORTH FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

NORTHEASTERN NEW YORK RADIOLOGICAL SOCIETY
Secretary, Dr. Anthony J. Tabacco, 621 Central Ave., Albany 6, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. Rob H. Kirkpatrick, 1219 28th St., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

Northwestern Ohio Radiological Society
Secretary, Dr. Anthony F. Lalli, 421 Michigan St., Toledo, Ohio.

Ohio State Radiological Society
Secretary, Dr. Chapin Hawley, 927 Carew Tower, Cincinnati 2, Ohio. Annual Meeting: Dayton, Ohio, May, 1963.

Oklahoma State Radiological Society
Secretary, Dr. Simon Pollack, Utica Square Medical Center, Tulsa, Okla. Meets in January, May and October.

Orange County Radiological Society
Secretary-Treasurer, Dr. Thomas J. Dorsey, 9922 Gilbert St., Anaheim, Calif. Meets fourth Tuesday of month except June, July, August and December in Orange County Medical Association Building.

Oregon Radiological Society
Secretary, Dr. James A. Schneider, St. Vincent Hospital, Portland 10, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. John N. Burkey, 555 Dental Bldg., Seattle, Wash. Annual meeting: Seattle, Wash.

Pennsylvania Radiological Society
Secretary, Dr. Frederick R. Gilmore, Clearfield Hospital, Clearfield, Pa. Annual meeting: Bedford Springs Hotel, May 23–25, 1963.

Philadelphia Roentgen Ray Society
Secretary, Dr. Antolin Raventos, 3400 Spruce St., Philadelphia 4, Pa. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Marvin Brodie, 3459 Fifth Ave., Pittsburgh 13, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

Radiological Society of Greater Cincinnati
Secretary, Dr. Richard B. Mulvey, 2421 Auburn Ave., Cincinnati, Ohio. Meets first Monday of each month at Cincinnati Academy of Medicine.

Radiological Society of Hawaii
Secretary, Major Michael A. Lopiano, 784 Hoomalimali St., Pearl City, Hawaii. Meets third Monday of each month at 7:30 P.M.

Radiological Society of Greater Kansas City
Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. Andrew F. Giesen, Ochsner Clinic, New Orleans 15, La. Meets annually during Louisiana State Medical Society meeting.

Radiological Society of New Jersey
Secretary, Dr. E. Arthur Kratzman, 912 Prospect Ave., Plainfield, N. J. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

Radiological Society of the State of New York
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y. Annual meeting to be announced.

Radiological Society of South Dakota
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
Secretary, Dr. Richard P. Storrs, 2131 West Third, Los Angeles, Calif.

Redwood Empire Radiological Society
Secretary, Dr. Lee E. Titus, 164 W. Napa St., Sonoma Calif. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Harry J. Pinsky, 386 Monroe Ave., Rochester 7, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting: Denver Hilton Hotel, Denver, Colo., Aug. 22–24, 1963.

San Antonio-Military Radiological Society
Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Tex. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
Secretary, Dr. Charles G. Campbell, 6673 Avenida Manana, La Jolla, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. Walter Coulson, San Francisco General Hospital, San Francisco 8, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 18, Calif.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Connecticut State Medical Society
Secretary, Dr. Wayne P. Whitcomb, Hospital of St. Raphael, New Haven, Conn. Meetings are held bimonthly.

Section on Radiology, Medical Society of the District of Columbia
Secretary, Dr. Martin A. Thomas, 1150 Connecticut Ave., Washington 6, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Southern Medical Association
Secretary, Dr. Robert D. Sloan, University Medical Center, 2500 North State St., Jackson 6, Miss. Annual meeting to be announced.

Section on Radiology, Texas Medical Association
Secretary, Dr. Frederick J. Bonte, University of Texas Southwestern Medical School, Dallas 35, Tex. Meets annually with the Texas Medical Association.

Shreveport Radiological Club
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

Society for Pediatric Radiology
Secretary, Dr. Richard G. Lester, Box 151, Medical College Station, Richmond, Va. Annual meeting: Queen Elizabeth Hotel, Montreal, Que., Canada, Oct. 7, 1963.

Society of Nuclear Medicine
Secretary, Mr. Craig C. Harris, Oak Ridge National Laboratories, Oak Ridge, Tenn. *Administrator*, Mr. Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting: Queen Elizabeth Hotel, Montreal, Que., Canada, June 26–30, 1963.

South Bay Radiological Society
Secretary, Northern Section: Dr. John S. Wilson, 1515 Trousdale Dr., Burlingame, Calif.; Southern Section: Dr. A. C. Mitchell, 728 Cass, Monterey, Calif. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

Southern Radiological Conference
Secretary, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala. Annual meeting: Grand Hotel, Point Clear, Ala., Feb. 1–3, 1963.

Southwestern Radiological Society
Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in the Paso del Norte Hotel.

Tennessee Radiological Society
Secretary, Dr. B. M. Brady, St. Joseph Hospital, Memphis, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas Radiological Society
Secretary, Dr. R. P. O'Bannon, 402 Professional Bldg., 1216 Pennsylvania Ave., Fort Worth 4, Tex. Annual meeting: San Antonio, Tex., Jan. 25 and 26, 1963.

Tri-State Radiological Society
Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evansville, Ind.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary, Dr. Richard Y. Card, St. Mark's Hospital, Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Vermont Radiological Society
Secretary, Dr. John R. Williams, 160 Allen St., Rutland, Vt.

Virginia Radiological Society
Secretary, Dr. Powell G. Dillard, Jr., 715 Church Street, Lynchburg, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Robert H. Rosenberg, 7011 38th Ave., N.E., Seattle 15, Wash. Meets quarterly.

West Virginia Radiological Society
Secretary, Dr. Karl J. Myers, The Myers Clinic-Broaddus Hospital, Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester Radiological Society
Secretary, Dr. Edward T. Bello, Westchester Academy of Medicine, Section on Radiology, Purchase, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary, Dr. Charles Benkendorf, 408 St. Francis St., Green Bay, Wis. Annual meeting each spring in various places.

Cuba, Mexico, Puerto Rico and Central America

Asociación de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
Secretary-General, Dr. Julio Toriello, 11 Calle 2–37, Zona 1, Guatemala. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de El Salvador
Secretary, Dr. Rafael Vaga Gómez.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

Sociedad de Radiología y Fisioterapía Cubana
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

Sociedad Costarricense de Radiologia
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

Sociedad Mexicana de Radiología, A. C.
Calle del Oro No. 15. México 7, D. F.
Secretary-General, Dr. E. Alvarez Hernández.
Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
Secretary, Dr. Jorge Carreras Girard, Suite 504, Profes sional Bldg., Santurce, Puerto Rico. Meets second Thurs day of each month at 8:00 P.M. at the Puerto Rico Medi cal Association Bldg. in San Juan.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
Secretary, Dr. Odilon Raymond, 5400 Blvd. Gouin. Quest, Montreal, Que., Canada. Meets four times a year.

British Institute of Radiology
Honorary Secretary, Dr. R. D. Hoare, 32 Welbeck St., London, W. 1, England. Meets monthly from October until May.

Edmonton and District Radiological Society
Secretary, Dr. S. C. Windle, 105 Northgate Bldg., Edmonton, Alberta, Canada. Meets first Tuesday of each month, October to May.

Faculty of Radiologists
Honorary Secretary, Dr. C. J. Hodson, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting: St. Bartholomew's Hospital, London, England, June 14–16, 1963.

Faculty of Radiologists, Royal College of Surgeons in Ireland
Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123 St. Stephens Green, Dublin 2, Ireland.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1, England.

Canadian Association of Radiologists
Honorary Secretary, Dr. Robert G. Fraser, *Associate Honorary Secretary*, Dr. D. J. Sieniewicz, 1555 Summerhill Ave., Montreal 25, Que., Canada. Annual meeting to be announced.

Montreal Radiological Study Club
Secretary, Dr. Leonard Rosenthall, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicale
General Secretary, Dr. Maurice Dufresne, 1560 Sherbrooke (East), Montreal, Que., Canada. Meets third Saturday each month.

Toronto Radiological Society
Secretary, Dr. Wallace M. Roy, St. Joseph's Hospitals, 30 The Queensway, Toronto 3, Ont., Canada. Meets second Monday of each month September through May.

College of Radiologists of Australia
Honorary Secretary, Dr. E. A. Booth, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

South America

Asociación Argentina de Radiología
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia
Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional del Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia
Secretary-General, Dr. Tede Eston de Eston, Caixa Postal 5984, São Paulo, Brazil.

Sociedad Argentina de Radiología, Junta Central, Buenos Aires
Secretary, Dr. Edgardo O. Olcese, Santa Fé 1171, Buenos Aires. Meetings are held monthly.

Sociedad Bolivana de Radiología
Secretary, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
Secretary, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia
Secretary, Dr. Alberto Mejía Diazgranados, Carrera 13, No. 25–31, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología y Fisioterapía
Secretary, Dr. Publio Vargas P., Casilla 1242, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología
Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia
Secretary, Dr. Luis Pinillos Ganoza, Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologia del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41–110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiologia de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenologia y Medicina Nuclear de la Provincia de Córdoba
Secretary-General, Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina.

Sociedad Venezolana de Radiología
Secretary-General, Dr. Rubén Merenfeld, Apartado No. 9362, Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets in February, March, May, June, October, November and December.

Société Française d'Electroradiologie Médicale, and its branches: Socété du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.
Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 8e, France.

Československá Společnost pro Roentgenologii a Radiologii
Secretary, Dr. Robert Poch, Praha 12, Šrobárova 50, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Deutsche Röntgengesellschaft
Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut., Lagenbeckstr. 1, Mainz, Germany. Annual Congress: Baden-Baden, Germany, April 24–28, 1963.

Società Italiana di Radiologia Medica e di Medicina Nucleare
Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Electrologie en Röntgenologie
Secretary, Dr. J. R. von Ronnen, Violenweg 14, den Haag, Netherlands.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear
Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

Schweizerische Gesellschaft für Radiologie und Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

Asia

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

Indonesian Radiological Society
Secretary, Professor Sjahriar Rasad, Taman Tjut Mutiah 1, Djakarta, Indonesia.

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ROENTGEN DIAGNOSIS

Abdomen

Beargie, Richard J., Hodgson, John R., Huizenga, Kenneth A., and Priestley, James T. Relation of cholangiographic findings after cholecystectomy to clinical and surgical findings. *Surg., Gynec. & Obst.*, Aug., 1962, *115*, 143–152. (From: Sections of Roentgenology, Medicine, and Surgery, Mayo Clinic and the Mayo Foundation, Rochester, Minn.)

The authors stress that biliary tract surgery on patients with vague symptoms and lacking clear cut pathology is fraught with failure. They report their experience with intravenous cholangiography in the evaluation of patients with symptoms referable to the upper abdomen following cholecystectomy at the Mayo Clinic in a 30 month period.

The technique of preparation and injection of 20 ml. of 52 per cent solution of iodipamide (cholografin) and subsequent laminagraphic exposures is described in detail. The cholangiograms were classified as normal, abnormal, or indeterminate. Correlation of satisfactory visualization of the biliary tree was found to be most reliably related to the values for direct-reacting serum bilirubin.

A total of 224 patients underwent common duct exploration of which 143 had satisfactory cholangiographic studies. Of 42 roentgenograms reported as normal, 7 were found to represent organic disease, while in 101 abnormal roentgenograms, 7 errors of diagnosis were recorded and the authors discuss these points. It appears that, given a satisfactory choledochogram, alert interpretation should provide an accurate diagnosis in 90 to 95 per cent of the cases.

Common ducts dilated by previous obstruction do not always return to normal size so that it is important to know the previous size of the duct in evaluating the dilatation. In attempting to determine the significance of dilatation, it is necessary to know the normal variations which Ferris and Vibert found to average 8.8 mm. in 112 patients at surgery. The authors found in 50 patients with cholecystectomy and without pathologic change on cholangiograms that the average diameter was 5.6 mm. They also present a table of measurements noted with various other surgical diagnoses.

The authors, in conclusion, comment on the problem of cystic duct remnant and its relation to symptoms, on the differential diagnosis of acute primary pancreatitis and acute obstructive cholecystitis, and on the diagnosis of obstruction at the sphincter of Oddi.

There are 4 laminagraphic reproductions with free hand drawings to illustrate their findings. The article should be read in the original.—*Richard E. Kinzer, M.D.*

Gynecology and Obstetrics

Dunn, P. M., Fisher, A. M., and Kohler, H. G. Phocomelia. *Am. J. Obst. & Gynec.*, Aug. 1, 1962, *84*, 348–355. (Address: Dr. H. G. Kohler, Birmingham Maternity Hospital, Birmingham 4, England.)

During 1961, the authors observed 4 phocomelic infants, but only 3 were born in the Birmingham Maternity Hospital. During the 10 year period from 1951 through 1960, although there were 21,065 births, no cases of phocomelia were noted. Lenz has estimated that between 2,000 and 3,000 cases of phocomelia were born in Germany since 1959. The evidence strongly suggests that the new teratogenic agent was thalidomide.

The essential characteristic of phocomelia is stunting or aplasia of the proximal portion of a limb, with more or less normal development of hands and feet. Two major morphologic patterns have been noted. In one group only the upper extremities are affected. This is consistent with the definition noted in the British Medical Dictionary. The second group consists of the babies with involvement of all four limbs but with more severe deformities of the upper limbs. Other congenital anomalies are usually associated.

In the authors' series of 3 cases, the mothers had roentgenographic examination late in pregnancy. The diagnosis of phocomelia was made in the second case. In the first case, the absence of the arms from one of the twins was apparent subsequently, but it was not noted in the beginning. In the third, only a lateral roentgenogram was made and this failed to show the fetus clearly. In the cases involving the lower limbs, persistent breech presentation occurred. In the few cases of phocomelia in which the lower limbs were normal, the vertex presented.

In November, 1961, no report of the association between phocomelia and thalidomide had appeared in the British literature. When thalidomide was withdrawn from the market at the end of 1961, the authors re-opened the investigations of these cases of phocomelia. In 2 of the cases thalidomide was taken early during pregnancy. In the remaining case it was not regarded as significant that thalidomide was given during the few days prior to delivery; the authors were not able to determine with accuracy that thalidomide was administered during early pregnancy.—*J. N. Ané, M.D.*

Emerson, Donald J. Congenital malformation due to attempted abortion with aminopterin. *Am. J. Obst. & Gynec.*, Aug. 1, 1962, *84*, 356–357. (From: The Department of Obstetrics and Gynecology, Highland-Alameda County Hospital, Oakland, Calif.)

The antimetabolic effect of aminopterin has been utilized in the treatment of acute leukemia and cer-

tain metabolic diseases but serious side effects and toxicity have limited its clinical use. Severe bone marrow depression with leukopenia, thrombocytopenia, aplastic anemia, gastrointestinal disturbances, and alopecia have been noted.

Thiersch, in 1952, reported 12 cases of first trimester pregnancy in which aminopterin was used to induce abortion. In 9 of 12 cases fetal death was immediate and followed by spontaneous abortion. At autopsy these fetuses showed multiple congenital anomalies. In 1956, Thiersch reported 12 additional cases of aminopterin used to induce abortion. Six patients failed to abort and one went to term. This infant was anencephalic. Similar cases were reported by Meltzer, and by Warkany, Beaudry and Hornstein.

The author reports the case of a pregnant female who ingested 29 mg. of aminopterin in divided doses over a 10 day period of approximately 6½ to 8 weeks' gestation. She developed severe stomatitis, generalized skin eruption and her hair fell out in large quantities. A scout roentgenogram of the abdomen showed a trimester fetus with delayed ossification of the cranial bones. Hysterotomy was performed and a stillborn fetus was delivered. At autopsy the fetus showed strikingly abnormal findings.

Ossification of the parietal bones occurs from 2 nuclei which appear at about the seventh gestational week. The crucial period of development of the external ear is about the seventh week. The malformations present in the fetus were consistent with the period of ingestion of aminopterin.—*J. N. Ané, M.D.*

SALA, FRANCO, and TELLINI, PIERO. The metroplastic operation after Strassmann. *Am. J. Obst. & Gynec.*, Aug. 1, 1962, *84*, 390–396. (From: The Department of Obstetrics and Gynecology, S. Camillo Hospital, Rome, Italy.)

Following routine hysterosalpingography in all infertile patients after a second miscarriage, the authors are convinced that uterine malformation is one of the most frequent causes of repeated miscarriages. In the authors' series there were 60 patients whose clinical histories and gynecologic examinations aroused suspicion of uterine malformation. These were subjected to hysterosalpingography. In 32 patients or 53 per cent the roentgen examinations showed anomalies in the form of the uterine cavity.

After thorough study of each case, the metroplastic operation after Strassmann was performed in 26 patients. Paul Strassmann emphasized the importance of double uteri in infertility and miscarriage and conceived of an operation to join the two uterine cavities. In this way the uterus was rendered capable of performing its reproductive function.

Of the 26 patients, only 18 returned for hysterosalpingographic checkups; 3 became pregnant a short time after the operation and therefore could not receive a checkup. Of the 21 cases: (1) 8 pregnancies carried to term with spontaneous delivery (7 with living babies; 1 case of fetal death during labor, cause not determined); (2) 2 pregnancies were established and not yet carried to term; (3) 4 cases of premature delivery between seventh and eighth month pregnancy (with 2 living babies); (4) 2 patients with 2 to 4 years having elapsed without pregnancy; and (5) 3 miscarriages during the first 3 months and 2 pregnancies carried to term with cesarean sections.

The authors believe that in the case of the cesarean sections, fear, aggravated by slight fetal distress and strenuous labor, resulted in the sections. The Strassmann operation *per se* does not constitute an indication for cesarean section as the scar is localized on the bottom of the uterus and has a greater resistance than the one left by cesarean section. Cesarean section is indicated only for factors not connected with the Strassmann operation.—*J. N. Ané, M.D.*

SIEGLER, ALVIN M. Synechiae of the uterine cavity after curettage; clinical and roentgenographic study of 5 cases. *Am. J. Obst. & Gynec.*, June 15, 1962, *83*, 1595–1598. (From: Department of Obstetrics and Gynecology, State University of New York, Downstate Medical Center, College of Medicine, and the Beth El Hospital, Brooklyn, N. Y.)

The true incidence of intrauterine adhesions which form after curettage has been difficult to ascertain. Asherman reported its occurrence in 68 per cent of women who had two or more curettages. Halbrecht noted a similar abnormality in 26 women who had 3 or more repeated abortions and found it to be the second most common cause of habitual abortion. Topkins analyzed 25 cases but did not cite the incidence in his series.

The lesions could result from some postoperative reactive fibrosis associated with a mild infection. These adhesions occur spontaneously and have been reported in cases of tuberculous endometritis and with submucous myoma. The clinical importance of traumatic synechiae as a cause of amenorrhea, infertility, and habitual abortion is mentioned.

Although the shadows seen on the hysterogram are characteristic, definitive proof of the existence of adhesions in each case is difficult to obtain without operation. Since there are certain errors in the interpretation of the hysterogram, an additional modality for the confirmation of the adhesions is important.

The type of therapy must be tempered by the history and clinical symptoms. Surgical extirpation of the lesion in the absence of menstrual irregularities or repeated abortion does not appear to be warranted. Originally Asherman advocated anterior hysterotomy but more recently he suggested the use of endocrine products and a generally more conservative approach.—*Eugene J. McDonald, M.D.*

Topkins, Paul T. Traumatic intrauterine synechiae; the Asherman syndrome. *Am. J. Obst. & Gynec.*, June 15, 1962, *83*, 1599–1608. (From: Brooklyn Women's Hospital and the Department of Obstetrics and Gynecology, State University of New York, Downstate Medical Center, Brooklyn, N. Y.)

In 1950 Asherman presented evidence that curettage or packing of the postabortal or postpartum uterus could induce formation of synechiae within the body of the uterus, a far more common site than the internal os. By means of hysterosalpingography he demonstrated that intrauterine synechiae represented regional obliteration of the uterine cavity, a result of conglutination of apposing surfaces of myometrium. He described the filling defects produced by synechiae as being single or multiple; very small or very large; round or long; in the shape of a window, heart, or tree; or very bizarre in contour. He stated that such shadows might be interpreted as polyps, fibroids, septa, or air bubbles. Characteristically, however, the shadows of synechiae could not be effaced by increasing the intracavitary pressure of the injected contrast medium.

Asherman concluded that the diagnosis of intrauterine synechiae could be made only by hysterosalpingography. He postulated that a uterine cavity which was distorted by extensive synechiae would provide a poor site for nidation and would therefore make sterility or abortion inevitable. At the same time, however, he recognized that patients with intrauterine synechiae exhibited a tendency for abortion even before the uterus had been damaged by curettage.

In the majority of instances subjective complaints are absent and the unsuspected condition is disclosed by the typical filling defects seen in the hysterogram. In 20 per cent, however, some degree of menstrual insufficiency exists. Intrauterine synechiae do not affect the patient's ability to become pregnant but are associated with a high incidence of repeated abortion, premature delivery, abnormal presentation of the fetus, and abnormal implantation of the placenta. Although some isthmic synechiae yield to simple dilatation of the internal os, almost all intrauterine synechiae are most effectively treated by digital separation through an abdominal hysterotomy incision.—*Eugene J. McDonald, M.D.*

Beringer, E. Duane, Hunter, James S., Jr., Welch, John S., and Scanlon, Paul W. Intracavitary use of radium for treatment of atypical uterine bleeding in women of menopausal age. *Am. J. Obst. & Gynec.*, July 1, 1962, *84*, 129–131. (From: The Section of Obstetrics and Gynecology, the Section of Surgery, and the Section of Therapeutic Radiology, Mayo Clinic and Mayo Foundation, Rochester, Minn.)

Radium was used to induce artificial menopause in a group of 364 women for the treatment of benign uterine bleeding. From 1944 to 1948, 306 patients were treated by this method and from 1954 to 1958, 58 were treated. Most patients were in the 40 to 59 year age group. The major indications for the use of radium were menorrhagia, menometrorrhagia, metrorrhagia and postmenopausal bleeding. Of the total patients treated during 1954 to 1958, 22.5 per cent were postmenopausal in comparison with 8.2 per cent in the earlier series, indicating that a different program of treatment for these patients had evolved in the interval. Preliminary dilatation and curettage was always performed to exclude malignancy. A total radium dose of 1,200 mg. hours was used.

The results showed that 12.3 per cent had had recurrent bleeding after radium treatment. Five patients subsequently developed adenocarcinoma of the fundus 13 months to 12 years following radium treatment.

At present, the initial treatment is dilatation and curretage followed by hysterectomy should abnormal bleeding persist. Radium therapy is reserved for a few selected patients.—*F. P. Shea, M.D.*

Genitourinary System

Kreel, Louis. Radiological aspects of nephrocalcinosis. *Clin. Radiol.*, July, 1962, *13*, 218–223. (From: The Department of Diagnostic Radiology, University College Hospital, London, W.C.1, England.)

The term nephrocalcinosis is usually confined to diffuse renal calcification detectable roentgenologically, as contrasted with deposits of calcium in the kidney in localized or circumscribed areas occurring in hypernephroma, tuberculous disease or renal infarction. In nephrocalcinosis the calcium deposit is usually situated in the medullary portion of the kidney, very rarely in the cortex.

In about 80 per cent of cases, hyperparathyroidism, hyperchloremic or renal tubular acidosis, idiopathic calciuria, medullary sponge kidney (congenital pyelectasia) or sarcoidosis will be found to account for nephrocalcinosis. There is no correlation between the degree of hypercalcemia which may be present and the degree of nephrocalcinosis. Hypercalcemia is probably the cause of impaired renal function and not the presence of interstitial calcification in the kidneys. Apparently there is no relationship between the degree or presence of nephrocalcinosis and renal function. The presence of chondroitin sulphate in all tissues undergoing calcification, cartilaginous, arterial and renal, suggests that this may be a common "calcifiability" factor.

While biochemical investigation is necessary in diagnosis of the etiology of nephrocalcinosis, various roentgen appearances may be helpful. A fine pinpoint stippling in the cortex and between the pyramids is very rare but is, nevertheless, suggestive of glomerulonephritis. Fine opaque streaks along the line of the ducts of Bellini may be found in hyperparathyroidism. In medullary sponge kidney one is apt to see small (5 mm. or less) round or ovoid calcium deposits with clear cut margins in the papillary portion of the renal pyramid. In renal tubular acidosis or hypercalciuria, nephrocalcinosis may be associated with large staghorn calculi.

Small kidneys tend to carry a poor prognosis in nephrocalcinosis as well as in other conditions, but normal-sized kidneys offer a relatively good prognosis. Thus, diseases such as hyperparathyroidism, sarcoidosis and Cushing's disease which produce hypercalcemia are associated with small kidneys (resulting from renal damage), often with absent or slight nephrocalcinosis. On the other hand, marked nephrocalcinosis with normal renal function and normal calcemia, with normal to large kidneys, may be seen in diseases producing hypercalciuria such as renal tubular acidosis and idiopathic hypercalciuria. —*Samuel G. Henderson, M.D.*

RICHARDSON, R. E. Nephrocalcinosis with special reference to its occurrence in renal tubular acidosis. *Clin. Radiol.*, July, 1962, *13*, 224–230. (From: The Diagnostic X-Ray Department, Bristol Royal Infirmary, Bristol, England.)

Nephrocalcinosis has been defined as "renal calcinosis marked by the precipitation of calcium phosphate in the kidney tubules" (Blakistone). This may consist of the typical striated appearance where one can be certain that not only is the calcification parenchymal but also tubular. This characteristic pattern, however, may be absent and one may see mottled areas of calcinosis with no obviously striated arrangement. In the absence of a spiculated appearance typical of tubular calcification, the calcification may be within the lesser calyces, the pyramids, or a combination of both. To use the term to signify parenchymal calcification would require the inclusion of tuberculous, neoplastic, and other rare forms of calcification as etiological factors. These usually give rise to a different pattern of calcification.

Nephrocalcinosis may arise (a) in disorders associated with hypercalciuria and/or hypercalcemia; (b) in conditions where the biochemical or physical conditions favor the deposition of calcium and where hypercalcemia does not necessarily coexist.

The author lists 3 groups of disorders giving nephrocalcinosis. Group A includes hyperparathyroidism, renal tubular acidosis, Cushing's syndrome, cortisone therapy, sarcoidosis, multiple myelomatosis, carcinomatosis, idiopathic hypercalciuria and hypervitaminosis. Group B includes necrotizing papillitis, medullary sponge kidney, drugs (sulfonamides and alkalies). Group C includes idiopathic cases. Since metabolic changes resulting in calcium loss may produce osseous changes, if such changes are apparent on roentgenograms and if the pattern is specific, then the radiologist is able to determine the cause of nephrocalcinosis; but if the changes are simply a loss in bone density, the radiologist may infer that the condition is likely to be caused by one of the disorders listed in Group A. In Group B a roentgenologic diagnosis can be reached only by noting the presence of renal changes, other than the calcinosis. In excretion urography the presence of dilated tubules in the region of the papillae would suggest the diagnosis of a "sponge kidney."

In this report 13 cases are described, 10 belonging to Group A, 1 to Group B, and 2 to Group C. In renal tubular acidosis many etiologic factors are responsible but the essential biochemical features are a systemic acidosis in conjunction with an alkaline urine. The acidosis, by creating a demand for base, results in the withdrawal of calcium and other basic ions from the body by kidney elimination. The alkaline reaction of the tubular contents reduces the solubility of the calcium which, as it is present in excessive amounts, is readily precipitated. This may result in a combination of nephrocalcinosis and osteomalacia. In sarcoidosis the nephrocalcinosis arises from the hypercalcemia which may be present in 45 per cent of all cases. This high blood calcium is probably the result of excessive calcium absorption due to the formation of a vitamin D-like substance. Idiopathic hypercalciuria differs biochemically from primary hyperparathyroidism only in the absence of hypercalcemia. Medullary sponge kidney which is of congenital origin is due to a disordered arrangement of the tubules in the region of the pyramids. The tubules become dilated or cystic and calcium deposition readily and often occurs.

Of the 13 cases of nephrocalcinosis reported, a definite or presumptive diagnosis was obtained in 11 cases. In 5 the diagnosis could have been reached or suspected solely on roentgenologic grounds. These 5 include 2 proven instances of hyperparathyroidism, 1 case of sarcoidosis, 1 case of renal acidosis and 1 case of medullary sponge kidney. A chest roentgenogram was of prime importance in the case of sarcoidosis. In hyperparathyroidism the detection of subperiosteal bone resorption is of the greatest value diagnostically. In renal acidosis the natural history of the nephrocalcinosis is of interest. Resolution of the areas of calcinosis may take place very rapidly after alkali treatment has been instituted. Curiously enough staghorn calculi may increase in size at a time when the calcinosis is resolving. It is likely that there is a tendency for the areas of calcinosis to fuse, the process being similar to the microscopic fusion of calcified foci.—*Samuel G. Henderson, M.D.*

Bateson, Eric M. Nephrocalcinosis in children: review of the literature and report of a case complicated by Wilms' tumour. *Clin. Radiol.*, July, 1962, *13*, 231–237. (Address: X-Ray Department, The City General Hospital, Sheffield, England.)

In 1934, Albright and his associates first used the term nephrocalcinosis to describe diffuse calcium deposits in and around the collecting tubules of the kidneys in a patient with primary hyperthyroidism. The calcium deposits are found in the cytoplasm and basement membrane of the collecting tubules and in the interstitial tissue between the tubules. Renal tubular calcification may be demonstrated both histologically and roentgenologically. Nephrocalcinosis is uncommon in children, the author having found less than 55 published cases in a survey of the literature. In the majority of cases the nephrocalcinosis was due to one of three conditions: idiopathic renal tubular acidosis of infancy; idiopathic hypercalcemia; and Albright's syndrome—the first two occurring only in children.

In idiopathic renal tubular acidosis of infancy, there is an inability of the renal tubules to reabsorb bicarbonate. This results in an increased urinary carbon dioxide content (neutral or alkaline urine) and a low serum carbon dioxide combining power (systemic acidosis). This combination of biochemical features is diagnostic. The loss of bicarbonate in the urine causes a drain on the base stores of the body, with calcium being mobilized from the bones and excreted in the urine, resulting in renal tubular calcification.

Idiopathic hypercalcemia is considered due to a hypersensitivity to vitamin D. The hypercalcemia is probably responsible for the presence of renal tubular calcification and ectopic soft tissue calcification. Bone changes may be seen roentgenographically consisting of increased density of the skull base; increased density around the orbits, around the periphery of vertebral bodies, carpals, tarsals and pelvis; and bands of increased density in the metaphyses.

In Albright's syndrome the essential metabolic disturbance is similar to that found in idiopathic renal tubular acidosis of infancy, but it differs in its course and often appears in later life. It is characterized by acidosis, rickets, demineralization of bones and dwarfism in children. Nephrocalcinosis is invariably demonstrable roentgenographically.

The author reports a case in a child of nephrocalcinosis complicated by a Wilms' tumor. The nephrocalcinosis could have been the result of undiagnosed renal acidosis of infancy, idiopathic hypercalcemia which had resolved by the time the child came under observation because of the Wilms' tumor, or some other factor, at present unknown. In this case and in 2 other reported cases of nephrocalcinosis without obvious cause, important clinical features were unexplained polyuria and polydipsia.—*Samuel G. Henderson, M.D.*

Loeschke, Adalbert. A congenital syndrome of retarded growth and anomalies of the urinary system but normal kidney function. *German Med. Monthly*, May, 1962, *7*, 149–151. (From: The University Children's Clinic of West Berlin, West Berlin, Germany.)

The author reports in detail 3 cases of dwarfism with congenital anomalies of the urinary tract. All 3 patients were males; had no impairment of renal function as determined by urinalysis and blood chemistries; had normal genitalia, normal endocrine function and delay in development with aggressive tendencies. Two had short metacarpals with normal bone age; one had slightly delayed bone age with normal metacarpals. The urinary tract anomalies in the 3 cases consisted of: (1) a relatively large bladder, right double collecting system with pyeloureterectasis, and a normal left kidney and ureter; (2) double right collecting system with a bladder diverticulum; and (3) aplasia of the left kidney.

The author cites an incidence of from 1 to 12 per cent of anomalies of the urinary tract; the relatively common occurrence in undersized children raises the question of coincidence of these anomalies.

In support of the syndrome theory, he cites a reported syndrome in mice of dwarfism, urogenital, skeletal and intestinal anomalies. Similarly, a breed of hamsters is small and shows an increased incidence of genitourinary abnormalities. The histologic pattern of an anomalous hamster kidney and the above aplastic left kidney were compared and found to be similar.—*Richard M. Colbert, M.D.*

Marshall, Frederick C. How long does it take a child's kidney to drain after retrograde pyelography? *J. Urol.*, May, 1962, *87*, 730–736. (From: The Columbia-Presbyterian Medical Center, The Squier Urological Clinic, New York 32, N. Y.)

In this article, the author has obtained data about drainage from the upper urinary tract under a variety of normal and abnormal conditions. He has studied 11 pediatric urologic patients between the ages of 4 and 12 years and evaluated the trapping roentgenograms with and without anesthesia, with and without dehydration, and with and without the effect of gravity.

In a normal upper urinary tract with the patient dehydrated and anesthetized, complete drainage from the upper urinary tract occurred between 15 and 30 minutes. In the abnormal upper urinary tract under similar conditions, drainage was delayed by 2 hours or more. With hydration, increased urinary flow, and also with the benefit of gravity, the trapping of contrast medium in the upper urinary

tract was much less marked. The upper urinary tract in children empties faster in the unanesthetized patient.

Such factors as the volume of the collecting system, the urinary output, the amount of obstruction, the gravity factor, and the age of the individual must be considered in evaluation of the trapping roentgenogram.

As a result of the experience obtained in this series of patients, the author suggests the following standard technique. The child is dehydrated and given a general anesthetic. Cystoscopic examination and retrograde pyelography are performed in the usual manner. If the pyelograms are satisfactory, trapping roentgenograms are obtained at 15 and 30 minute intervals. If contrast medium is still visible on the 30 minute roentgenogram, further delayed roentgenograms should be ordered at 1 or 2 hours and even up to 24 hours as indicated.—*George W. Chamberlin, M.D.*

MACEWAN, D. W., DUNBAR, J. S., and NOGRADY, M. B. Intravenous pyelography in children with renal insufficiency. *Radiology*, June, 1962, *78*, 893–903. (Address: Dr. D. W. MacEwan, Montreal Children's Hospital, 2300 Tupper Street, Montreal 25, Quebec, Canada.)

The authors report the results of a study to determine the value of excretory pyelography in infants and children with renal insufficiency. The records of the Montreal Children's Hospital from July 1, 1951 until July 1, 1961 were searched and all those showing nonprotein nitrogen values over 45 mg. per 100 cc. of blood were selected. The charts and the films of all the children who had intravenous pyelograms were reviewed. Eighty-nine patients were selected for this study; 54 were under 1 year of age. The azotemia was classified as prerenal, renal or postrenal on the basis of history, physical findings, laboratory tests, intravenous pyelography, and follow-up evaluation

The contrast agents used for the pyelographic studies were 35 per cent iodopyracet, 50 per cent sodium acetrizoate and currently 60 per cent diatrizoate methylglucamine. The intravenous dosage schedule was: up to 6 months, 10 cc.; 6 months to 2 years, 10 to 15 cc.; 2 years to adult life, 15 to 30 cc. Films were exposed at 3, 6, and 15 minutes. Lateral, prone, upright, and voiding roentgenograms were obtained. If the density produced by the first injection was inadequate, a repeat injection was done a few hours later. Voiding roentgenograms were made with patient cooperation or by automatically controlled exposure during micturition. The importance of good roentgenographic and dark-room technique is stressed. A cleansing enema was the only preparation; there was no restriction of food or fluid intake before the examination.

In prerenal azotemia good or adequate pyelograms were obtained in 20 of the 21 patients examined. Excretory urography was valuable to rule out renal or postrenal pathology. All 22 of the children with urinary infections had examinations of diagnostic quality. Chronic pyelonephritis did not interfere with good roentgenographic detail. In the 6 children with glomerulonephritis, the diagnostic quality of the studies varied inversely with the nonprotein nitrogen levels, high values being associated with poor pyelograms. The only failure occurred in a patient with a nonprotein nitrogen value of 105 mg. per cent. Structural anomalies were demonstrated in 12 cases. Pyelographic detail was generally poor and careful preparation of the patient and meticulous roentgenographic technique were necessary to show the abnormality. There were 3 patients with neurogenic abnormalities in the series. In postrenal abnormalities, simple obstruction was usually associated with good pyelograms, while children with vesicoureteral reflux tended to have poor pyelograms, probably due to secondary renal damage and dilution of the contrast agent.

There was one death, a very sick newborn infant who was shown at postmortem examination to have acute traumatic nephrosis. No other serious adverse effects were encountered.—*A. W. Sommer, M.D.*

WESTPHAL, ROBERT D., SCOTT, RUSSELL, JR., ERICKSON, ETHEL E., and MOTZKIN, DONALD. Scintillation scanning in renal disease. *J. Urol.*, Apr., 1962, *87*, 519–526. (From: The Departments of Medicine, Urology and Pathology of Baylor University College of Medicine and the Veterans Administration Hospital, Houston, Tex.)

The authors point out the limitations of various diagnostic procedures including urography, split renal function studies, angiography, renal biopsy, and radioisotope renography. The initial goal of this study was to develop a technique which would delineate early renal carcinoma. Subsequently, the problem has been broadened to include other focal lesions of the kidney. The theory and technique of renal scanning consist of the administration of radioactive material which is specifically concentrated by the normal tissue and can be detected by standard radiation recording devices. Radioactive I^{131} labeled hippuran is given intravenously and its gamma radiation is detected by the scintillation counter placed over the renal area on the movable recording device.

One hundred and thirteen renal scans were performed in 87 patients. The paper includes 5 detailed case studies with illustrative roentgenograms and renal scans. From the evidence noted in these cases, renal scanning is an additional valuable procedure for the urologist. The authors feel that pyelonephritis and diffuse vascular disease are indistinguishable in the renal scan. The renal scan must be correlated with the clinical findings and the pyelographic ap-

pearance for satisfactory diagnosis. The scan will give further information regarding acute and chronic pyelonephritis, tumor deformity, and congenital defects. In certain instances, it may yield information on ultimate prognosis of the disease. In the benign conditions, serial studies are especially important in patients with a changing status of their disease such as occurs in pyelonephritis.—*George W. Chamberlin, M.D.*

Horst, W., Rösler, H., Schneider, C., and Conrad, B. Radio-nephrography and renal scintigram; combined investigation of renal function and structure. *German Med. Monthly*, June, 1962, *7*, 186–188. (From: The University Departments of Radiology and Radiotherapy, Hamburg-Eppendorf, Germany.)

The aim of these investigators has been "to develop the use of radioisotopes so as to devise an accurate method for measuring renal function (nephrography) and a method for visualizing renal anatomy (renoscintigram)." In measuring renal function an intravenous injection of I^{131} diodone is made and the gradual decline of blood radioactivity is followed by a counter over the heart. At the same time, 2 counters follow the rise and fall in the renal areas. The heart curve count is reduced to the same scale and subtracted from the kidney curve. From this "difference curve" a "dead space" curve is subtracted to give the real extravascular component of the kidney. This is, in fact, that part of the renal parenchyma which is concerned with excretion.

To develop the renoscintigram for better anatomic mapping, the authors prepared Hg^{203} labeled mersalyl (Hg^{203} salygran, Hoechst). This isotope emits hard radiation which remains in the kidney for a reasonable period. The general body background is only 25–30 per cent of the gross counting rate over the kidney and by use of proper electronic equipment this background count can be accurately subtracted from the gross counting rate, thus giving a linear register of the true count.

The authors believe that a combination of these two tests is less expensive and makes smaller demands on the patient than roentgenologic examination plus clearance tests. In addition, the radiation hazard is less than that in pyelography.—*Richard E. Kinzer, M.D.*

Schlegel, J. U., Izenstark, J., O'Dell, R. M., and Cuellar, J. A technic for kidney scanning. *South. M. J.*, May, 1962, *55*, 471–474. (From: The Department of Surgery, Division of Urology, and the Department of Radiology, Tulane University School of Medicine, New Orleans, La.)

Acute obstruction of the ureters during the time of observation was done by catheter control. This caused intrapelvic pressure to rise to a point where kidney filtration ceased, while tubular secretion continued. Hippuran I^{131} was then given intravenously, and scans were obtained over the kidneys.

The authors state that with their technique it should be possible to detect nonfunctioning areas down to .5 cm. in size. Tumor detection, renal hypertension and focal pyelonephritis would be diagnosable by this method.—*David C. Alftine, M.D.*

Winter, Chester C., and Myers, William G. Three new test agents for the radioisotope renogram: DISA-I^{131}; EDTA-Cr^{51}; and Hippuran-I^{125}. *J. Nuclear Med.*, July, 1962, *3*, 273–281. (From: Departments of Surgery [Urology], Medicine and Radiology, Ohio State University Health Center, Columbus, Ohio.)

Studies on 3 new radioisotope renogram test agents, DISA-I^{131}, EDTA-Cr^{51}, and Hippuran-I^{125}, are reported. The desirable features as well as the disadvantages of each agent, in the making of renograms, are presented. DISA-I^{131} and EDTA-Cr^{51} are described as being excreted too slowly by the kidneys to be useful clinically in making standard renograms. Hippuran-I^{125}, on the other hand, is described as the agent of choice at the present time.—*Isaac Reese, M.S.*

Winter, Chester C., and Myers, William G. I-125, a new radioisotope for the labeled hippuran renogram. *J. Urol.*, July, 1962, *88*, 100–102. (From: The Departments of Surgery, Medicine, Physiology and Radiology, Ohio State University Health Center, Columbus 10, Ohio.)

Hippuran I^{125} is now recommended as the test agent of choice for making radioisotope renograms. This isotope produces soft photons of 27.2–35.4 kev. in comparison to the high energy photons of I^{131}. The low energy photons of I^{125} have several advantages that make them inherently directional. Thus the equipment can be smaller and lighter since there is no need for heavy lead collimators as used with I^{131}. Furthermore, the soft I^{125} photons are efficiently absorbed in "thin crystal" scintillation detectors that have a much lower background counting rate than those used previously for making renograms with hippuran I^{131}. Iodine^{125} does not emit useless and undesirable beta particles. Radiation exposures to the patient are lower since the dose can be considerably decreased from that used with I^{131}. This isotope has a half life of 60 days which makes for added convenience.

The authors report only a comparison of normal renograms but do not mention any of their experiences with the abnormal or diseased kidney. It would

be interesting to know if the relative values persisted under other circumstances.—*George W. Chamberlin, M.D.*

BOYARSKY, SAUL, KAPLAN, NEVILLE, MARTINEZ, JOSE, and ELKIN, MILTON. Cinefluorography of the urinary tract after ureteroileostomy. *J. Urol.*, Aug., 1962, *88*, 325–329. (From: The Urology Division, Department of Surgery, and Department of Radiology, Albert Einstein College of Medicine and Bronx Municipal Hospital Center, New York 61, N. Y.)

Cinefluorography of the urinary tract has been of considerable value in the study of the ileal segment and also of the upper urinary tract in patients after ureteroileostomy. The authors studied normal controls and patients with ileal conduits after intravenous injection of hypaque, and also after retrograde injection of sodium iodide solution. These patients were observed during fluoroscopy and cinefluorography. It was found by comparing the ileal loop before and after ileoureterostomy that the ileal segment did not change its physiologic nor mechanical characteristics after its isolation from the gastrointestinal tract and incorporation into the urinary tract. The isolated loops varied in their motility from a hyperactivity which ejected the catheter to a slow rhythmic motion with little peristaltic activity. All loops studied showed clinically satisfactory function with an adequate stoma. Reflux of contrast medium from the retrograde injection into the ileal loop was frequently noted. This reflux was very rapid and often filled the entire ureter shortly after injection.

The authors describe the motions of the collecting systems in both the normal and abnormal upper urinary tract when studied by the intravenous method. The rate and amplitude of activity in the calyceal system, pelvis, and ureter were roughly correlated with the degree of hydronephrosis. The pelvis and ureter were rarely seen in systole and early hydronephrosis could be demonstrated by diminution of the constant flux in the size and shape of the renal pelvis and calyces.

It is emphasized that the renal pelvis acts as a reservoir, and not as a detrusor organ, in both the normal and the hydronephrotic kidney. The ileal segment retains its basic functional characteristics after ureteral transplantation when it is being used as a urinary conduit.—*George W. Chamberlin, M.D.*

MALDONADO, JUAN. Comunicaciones fistulosas entre aparato urinario y aparato digestivo: presentación de cinco casos; revisión de la bibliografía. (Fistulous communications between the urinary and digestive tracts: presentation of five cases; review of the literature.) *Rev. urol., México*, Nov.–Dec., 1961, *19*, 357–381. (From: Unidad de Urología, Pabellon 5 del Hospital General, México, D. F.)

Five causes of fistulous communications between the urinary tract and intestine are listed: (1) foreign body; (2) congenital; (3) traumatic; (4) neoplastic; and (5) inflammatory. The clinical picture in a typical case shows pneumaturia, fecaluria, passage of urine through the rectum, polyuria, urgency, and occasionally, blood and suprapubic pain.

Procedures useful in confirming the diagnosis include endoscopy, sigmoidoscopy, visualization of the fistulous tract with contrast media, cystography and excretory urography. Treatment must be individualized, depending on the general condition of the patient, site of the lesion, etiologic cause of the fistula, etc.

Five cases are presented showing a fistulous communication between the lower intestinal tract and the urinary tract. The first cases was an epidermoid carcinoma of the cervix which invaded the urinary bladder and ileum; the second was an ureteral-rectal fistula following a periureteral abscess; the third followed invasion of the sigmoid colon by an epidermoid carcinoma arising probably from the bladder; and the last 2 cases causing fistulas were the result of diverticulitis of the sigmoid.—*Murray M. Friedman, M.D.*

ELKIN, MILTON. Supine and prone positions in intravenous urography for diagnosis of bladder lesions. *Radiology*, June, 1962, *78*, 904–912. (From: Albert Einstein College of Medicine, Eastchester Road and Morris Park Avenue, New York 61, N. Y.)

During urographic study a lesion of the bladder is more clearly visualized when it is put in the dependent position. Two factors are responsible for this: greater opacification due to a layering effect and stretching due to the weight of the contained fluid. The musculature of the bladder is in a state of plastic tonus and remains in this state until filling reaches the "average individual capacity." Then the plastic tonus changes over to a dynamic state, the beginning of the detrusor action. The plastic tonus exercises no pressure on the urine in the bladder, but the weight of the urine in the bladder exerts a force on its dependent portion resulting in a difference of bladder shape with change in position.

The author reports the results of studies utilizing these factors to obtain better visualization of bladder lesions. After the intravenous administration of the opaque medium (50 per cent hypaque), the author obtains anteroposterior urograms in the recumbent position at 5, 15, and 25 minutes, followed immediately by a 25 minute prone exposure. A 30 minute erect anteroposterior urogram is also taken. The prone view has been very helpful in demonstrating the presence and the position of abnormalities of the urinary bladder, especially lesions of the anterior

wall. Lesions of the posterior bladder wall are more clearly seen in the supine view.—*A. W. Sommer, M.D.*

Gosalbez, Rafael, and Gil-Vernet, Jose Maria. Bladder tomography: the use of air intra- and perivesically in the radiologic study of bladder tumors. *J. Urol.*, Aug., 1962, *88*, 312–317. (Address: Dr. R. Gosalbez, Rosellon 283, 2°, Barcelona, Spain.)

Double contrast studies when combined with tomography produce an image of bladder tumors which is valuable in the volumetric evaluation and estimation of the degree of infiltration.

The authors inject 250 cc. of air through a needle in the perivesical space just above the symphysis pubis. The urine is drained from the bladder by catheter and the bladder filled with air. Tomography is then utilized in the evaluation of the bladder wall and perivesical space.

Five cases of bladder tumors studied by this method are reported. The importance of this method is based upon the fact that the overlapping of opaque contrast medium in the spherical-shaped cavity, such as the bladder, hides many of the facets from the observer, whereas with two dimensional tomograms using air as a contrast medium, a more accurate definition of the bladder tumor can be made. In one instance a tumor undetected on ordinary cystograms and by cystoscopy was revealed by this method.—*George W. Chamberlin, M.D.*

Fetter, Theodore R., Yunen, Jose R., Greening, Roy R., and Benjamin, Alvin. Seminal vesiculography: diagnostic aid in prostatic carcinoma. *J. Urol.*, May, 1962, *87*, 718–725. (From: The Departments of Urology and Radiology, Jefferson Medical College Hospital, Philadelphia, Pa.)

Seminal vesiculography is recommended as a method for earlier differential diagnosis between benign hypertrophy and malignant disease of the prostate.

It is based upon the fact that the ejaculatory ducts, which are located in a symmetric position on either side of the midline, run through the prostatic substance. These ducts are separated from the prostate tissue by a wall which consists of a fibrous outer layer, a muscular medial layer, and a single layer of columnar mucous membrane. Their lumen is approximately 1.5 mm. in diameter and they have a length of approximately 15 mm. These ducts can be demonstrated roentgenographically by injection of approximately 2 cc. of renografin into the vas deferens.

This procedure was performed on 53 patients with subsequent histologic verification of the preliminary diagnosis. Benign prostatic hypertrophy was present in 32 cases and carcinoma of the prostate in 21. Two of the patients with benign prostatic hypertrophy had evidence of chronic prostatitis with prostatic calculi.

In those patients with benign hypertrophy of the prostate, the ejaculatory ducts were normal or dilated. In only one instance of this group, did the seminal vesiculogram show bilaterally narrowed ducts thought to reflect malignant disease. In this instance, no malignant tissue was found on histologic examination.

In all other instances where malignant disease was present, there were changes in the configuration of the ejaculatory ducts in contradistinction to those found in patients with benign hypertrophy. Patients with carcinoma, confined within the limits of the capsule, showed ejaculatory ducts which were either narrowed, elongated, rigid, or partially amputated. These changes occurred either bilaterally or unilaterally depending upon the extent and location of the disease. In the absence of previous surgery, such changes are not observed in benign prostatic hypertrophy.

The authors present 12 composite figures to illustrate their findings and conclude that seminal vesiculography appears to be a rewarding and accurate technique that should be considered in all patients undergoing vasectomy prior to prostatic surgery.—*George W. Chamberlin, M.D.*

Pendergrass, Henry P., Tristan, Theodore A., Blakemore, William S., Sellers, Alfred M., Jannetta, Peter J., and Murphy, John J. Roentgen technics in the diagnosis and localization of pheochromocytoma. *Radiology*, May, 1962, *78*, 725–737. (Address: Dr. Henry P. Pendergrass, Department of Radiology, Massachusetts General Hospital, Boston 14, Mass.)

A pheochromocytoma is a relatively rare functioning tumor arising from the chromaffin tissue of the adrenal medulla or from chromaffin tissue elsewhere in the body. Patients with this tumor may present with either paroxysmal or sustained hypertension and a wide variety of bizarre symptoms, all of which can be cured by surgical removal of the tumor if its site can be located. There are now available pharmacologic, chemical, and biologic tests for the detection of these tumors but false negative and false positive results are still being reported. Since these tumors may be multiple and extra-adrenal, lengthy surgical explorations are sometimes necessary. Because of this it is the authors' opinion that localizing roentgenography should be seriously considered whenever a pheochromocytoma is either suspected and not yet proven, or not accurately localized by preliminary examination.

Nine cases of pheochromocytoma have been diagnosed at the University of Pennsylvania Hospital in

the past 5 years. The procedures of choice for demonstrating the lesions have been perirenal carbon dioxide insufflation and percutaneous retrograde femoral aortography. Other investigators have preferred different localizing roentgengraphic methods and in order that a radiologist may designate or adapt a given procedure for a particular patient or problem, the other localizing roentgenographic methods are listed and briefly discussed. These roentgen techniques are as follows:

I. Roentgenograms without contrast media: abdomen, chest
II. Intravenous urography and retrograde pyelography
III. Nephrotomography, with or without pneumography
IV. Retroperitoneal pneumography
  (a) Presacral versus perirenal
  (b) CO_2 versus others
V. Aortography
  (a) Venous
  (b) Translumbar
  (c) Percutaneous retrograde femoral
VI. Aortography and pneumography
VII. Inferior vena cavography
VIII. Perirenal diodrast

I. *Survey of abdomen and chest.* The plain survey roentgenogram of the abdomen may show a suprarenal mass, giving a clue to the location and size of the tumor. Some investigators have used lateral and oblique roentgenograms of the abdomen plus laminagraphy to localize these tumors without the use of contrast media. Very rarely some curvilinear eggshell-type calcium or stellate calcification may be seen in a pheochromocytoma.

II. *Intravenous urography and retrograde pyelography.* These procedures may show displacement of a kidney or ureter due to a mass. Rarely, filling defects in the opacified urinary bladder have turned out to be pheochromocytomas.

III. *Nephrotomography.* Precisely timed injection of an intravenous contrast medium with laminagraphy at preselected levels may show a mass. This may be combined with perirenal air insufflation for further definition of a mass.

IV. *Retroperitoneal pneumography.* Presacral or perirenal injection of either air, oxygen or CO_2 may outline small suprarenal tumors. The authors prefer to use CO_2 which they feel is safer because of its greater solubility than air or oxygen in the blood stream. Laminagrams at predetermined levels, as well as anteroposterior and oblique roentgenograms are quickly obtained following injection of the CO_2 as the gas is absorbed very rapidly.

V. *Aortography.* This procedure may reveal a tumor not demonstrated by retroperitoneal pneumography. The converse is also true, because, as in the skull, arteriography and pneumography are complementary studies with one procedure outlining the tumor when the other does not. Rapid serial roentgenograms are of great importance when this technique is used. Of the 3 methods, venous, translumbar, and percutaneous retrograde femoral, the latter generally gives better results in the authors' experience.

VI. *Aortography and pneumography.* This combined procedure is used by some but is better when air is used because CO_2 is absorbed too rapidly.

VII. *Inferior vena cavography.* This fairly simple procedure may be of value when aortographic and pneumographic procedures fail to give a definite answer.

VIII. *Perirenal injection of opaque media.* This procedure using isotonic diodrast, saline, and hyaluronidase mixtures has been used by some but it is felt that it does not offer any advantage over perirenal gas.

In conclusion the authors feel that the experienced radiologist, with his special diagnostic techniques, may assist the clinician in confirming the presence of a pheochromocytoma when such a tumor is strongly suspected and when the various chemical and biologic diagnostic tests give confusing results. An extensive bibliography is presented, as well as many illustrations of the results of the various techniques.—*Donald N. Dysart, M.D.*

SKELETAL SYSTEM

BANKS, HENRY H. Factors influencing the result in fractures of the femoral neck. *J. Bone & Joint Surg.*, July, 1962, *44A*, 931–964. (From: The Departments of Orthopedic Surgery, Harvard Medical School and the Peter Bent Brigham Hospital, Boston, Mass.)

The author carefully analyzes a series of 213 displaced and 88 impacted intracapsular femoral neck fractures. The results of treatment were far superior in impacted fractures where 96.6 per cent showed union, than in displaced fractures where only 72.4 per cent showed union.

Of all the different anatomic types of displaced fractures, the wedge type is more likely to heal than the vertical beak type which resulted in 73.5 per cent of the nonunions. The factors involved in nonunion were mainly poor internal fixation and premature weight bearing. It was felt that comminution may play a significant role in nonunion, as well. Aseptic necrosis occurred in one-fourth of the patients with displaced and impacted fractures followed for more than 2 years in this series.

Most observers agree that adequate reduction of displaced fractures to either the anatomic or overcorrected valgus position is an important factor in obtaining a good result. For internal fixation of displaced fractures, the Smith-Petersen nail was preferred. The best position for the tip of the nail is within 1 cm. of the center of the articular surface and not more than 1 cm. deep to the articular surface. The use of a plate for additional fixation of the nail to

the shaft of the femur appeared to be advantageous in vertical fractures, especially if comminuted. Subcapital fractures in the valgus position and wedge fractures did not appear to need this additional fixation. Weight bearing should not be allowed until there is roentgenographic evidence that the fracture is healed.

The incidence of nonunion in displaced intracapsular femoral neck fractures can be decreased by: (1) accurate reduction; (2) accurately placed, adequate internal fixation; and (3) carefully supervised postoperative care.—*F. P. Shea, M.D.*

Maroteaux, Pierre, and Lamy, Maurice. La pycnodysostose. (Pycnodysostosis.) *Presse méd.*, Apr. 25, 1962, *79*, 999–1002. (From: Clinique de Génétique Médicale de la Faculté de Médecine, Hôpital des Enfants Malades, Paris 15e, France.)

A new variety of constitutional condensing osseous lesion, which the authors designate as pycnodysostosis, is described. Typically, these cases show diminished stature, pathologic fractures, failure of the posterior fontanelles to close, and shortness of hands and feet.

The roentgenologic studies reveal generalized skeletal condensation, widening of the cranial sutures, loss of the mandibular angle, and a partial aplasia of the fingers and toes.

The study of these and other cases culled from the literature indicates that there is a recessive hereditary factor.—*Frank A. Riebel, M.D.*

Mozes, Mark, Ramon, Yochanan, and Jahr, Joseph. The anterior tibial syndrome. *J. Bone & Joint Surg.*, June, 1962, *44A*, 730–736. (From: The Department of General and Vascular Surgery, Government Hospital, Tel-Hashomer, Israel.)

The etiology of the anterior tibial syndrome is either functional or anatomic. The functional type is related to overexertion in young adults, frequently army recruits, unaccustomed to sustained exercise. It is caused by acute ischemia of the tissues in the anterior tibial compartment. No vascular lesion is found by arteriography in these cases.

Eight cases of the anatomic type are reported. These were characterized by the sudden onset of progressively increasing pain in the pretibial region and the inability to walk. The anterior tibial compartment was under tension and all leg muscles were tender. The affected limb was cool, bluish and pale. Erythema usually occurred over the pretibial region and was most apparent when the legs were dependent. The pulses of the popliteal, posterior tibial and corsalis pedis were absent. In some patients even the pulsations of the femoral artery were absent. Foot drop and loss of sensation over the dorsum of the first two toes consistently developed in all patients.

The lesion progressed to necrosis of all the contents of the anterior tibial compartment regardless of the treatment rendered. Anterior tibial fasciotomy helped restore collateral circulation in the remainder of the limb by relief of reflex spasm but did not influence the final outcome.

The cause of the obstruction in this series of patients was trauma in 4 cases, thrombosis in 2 and embolism in 2. The location of the obstruction was the common iliac artery in 1, the femoral artery in 5 and the popliteal artery in 2 patients. Arteriograms demonstrated the arterial lesion in all cases. The impaired circulation apparently causes venous stasis and swelling of all the muscle contents of the compartment. This further embarrasses the blood supply and results in stasis of metabolic products. Following fasciotomy to relieve this tension, reconstitution of the blood supply by embolectomy, vascular suturing or grafting is indicated.—*D. Morse, M.D.*

Dunn, Adolphus W., and Aponte, Gonzalo E. Congenital bowing of the tibia and femur: case report with autopsy findings. *J. Bone & Joint Surg.*, June, 1962, *44A*, 737–740. (From: The United States Naval Hospital, Guam, Mariana Islands.)

A case is presented of congenital bowing of both tibiae and the left femur in an infant who died of renal insufficiency 37 hours after birth. Hydrocephalus, syndactyly and anomalies of the urinary tract were noted. Marked narrowing of the medullary cavities of the shafts was also noted at the apices of the bowing. This was associated with considerable cortical sclerosis and periosteal thickening. The theory that this represents a growth aberration involving a considerable portion of the shaft with a failure to produce normal bone is supported.—*D. Morse, M.D.*

Garn, Stanley M., and Rohmann, Christabel G. Parent-child similarities in hand-wrist ossification. *A.M.A. Am. J. Dis. Child.*, Apr., 1962, *103*, 603–607. (From: Department of Growth and Genetics, Fels Research Institute, Yellow Springs, Ohio.)

Observations on hand-wrist skeletal maturation were made covering 2 generations and involving 36 parents and 72 children. Since none of the 36 parents married a fellow participant, the parent-child comparisons refer to one parent only. Roentgenograms were made from ages 1.0 through 5.0 years, apparently at 6 month intervals, and great care was taken that this was done within narrow tolerance limits on birthdays and half birthdays. The mean duration between roentgenograms taken on the parent and corresponding age of the child was 24 years.

There was a definite significant correlation in time

of appearance of specific ossification centers of parent and child. Parents who were "advanced" in hand-wrist ossification by recognized standards at a given age tended to have children who were also advanced at the same age. This was also true for parents with "delayed" ossification.

These familial similarities were best correlated with the carpal, distal radial and ulnar ossification centers. The digital and metacarpal epiphyses did not correlate nearly so well genetically.

The authors conclude that in analyzing hand-wrist ossification data it would be feasible to minimize information gained from the carpal centers and maximize reliance on digital and metacarpal centers.—*R. Lynn Turner, M.D.*

DUNN, FRED H. Apert's acrocephalosyndactylism. *Radiology*, May, 1962, *78*, 738–742. (From: Michael Reese Hospital, 29th Street and Ellis Avenue, Chicago 16, Ill.)

The association of coronal suture synostosis (acrocephaly) and syndactylism was first described by Apert in 1906. Since that time only about 100 cases of acrocephalosyndactylism have been reported, none in American radiologic journals.

The author reports a case in a Negro female child, followed for 9 years, with particular attention to the roentgenologic features.

Characteristically the calvarium is lengthened vertically, shortened anteroposteriorly and broadened transversely. The frontal region is prominent and bulging. There is synostosis of the coronal suture, with the resulting increased intracranial pressure manifested by digital markings on the inner table of the calvarium. The posterior and middle cerebral fossae are not only shortened in their anteroposterior diameters but are abnormally deep. The orbital fossae are oblique and shallow, giving the palpebral apertures an antimongoloid tilt. There is hypoplasia of the facial bones with hypoplastic maxillae. The mandible is usually normal sized, giving an appearance of relative prognathism.

Syndactylism is generally symmetric and usually involves all 4 extremities. The degree of involvement varies from partial fusion of the skin to fusion of both bone and skin.

The cause of acrocephalosyndactylism is generally agreed to be a defect in germ plasm. The development and intelligence of children affected with this disease are usually normal, as is their life span.—*Ralph Bowman, M.D.*

TZE, KHONG BAN. A case of parathyroid osteodystrophy. *Singapore M. J.*, Mar., 1962, *3*, 25–29. (From: The Department of Orthopaedic Surgery, University of Singapore, Singapore.)

The author presents a case of parathyroid osteodystrophy due to a single adenoma of the right inferior parathyroid gland. The patient was a 23 year old cabinet maker with pain in the back. He had generalized osteoporosis with coarse trabeculation. There was cyst formation in the left radius with posterior bowing. There were large rarefied areas in the proximal femora with cortical thinning. The bones of the hands and feet demonstrated many small areas of rarefaction, with periosteal thickening of many phalanges. There was a "moth-eaten skull." Dental roentgenograms showed a "ground-glass" pattern between the teeth, with loss of lamina dura. There were no renal calculi. There was no soft tissue calcification. The barium swallow study was normal.

The blood biochemistry showed high serum calcium, low serum inorganic phosphate, elevated blood alkaline phosphatase, and increased urinary calcium output.

The tumor was excised with an uneventful postoperative course. The case has been followed for two years; the calcium and phosphorus levels have returned to normal.

The author gives extensive laboratory data, and includes four good roentgenographic reproductions.—*Delano Z. Arvin, M.D.*

BLACKARD, WILLIAM G., ROBINSON, ROSCOE R., and WHITE, J. EARLE. Familial hypophosphatemia: report of a case, with observations regarding pathogenesis. *New England J. Med.*, May, 1962, *266*, 899–905. (From: The Departments of Medicine, Duke University Medical Center and Veterans Administration Hospital, Durham, N. C.)

Report of a family showing hereditary transmission of familial hypophosphatemia is well illustrated by suitable lineage graphs, roentgenographic reproductions, laboratory procedures, etc.

The patient presented as the propositus showed a suppression of elevated phosphate clearance values, and the rise of maximum tubular reabsorption of phosphate after a calcium infusion, designed to suppress secretion of endogenous parathyroid hormone. This indicates either a causative or permissive role of the parathyroid glands.

The authors claim additional support to the theory that secondary hyperparathyroidism, probably owing to decreased intestinal absorption of calcium, is indeed the cause of familial hypophosphatemia.—*David C. Alftine, M.D.*

SILVERMAN, JEROME L. Apparent dominant inheritance of hypophosphatasia. *A.M.A. Arch. Int. Med.*, Aug., 1962, *110*, 191–198. (From: Department of Pathology, Washington University School of Medicine, Euclid Avenue and Kingshighway, St. Louis 10, Mo.)

The syndrome hypophosphatasia is one of the in-

born errors of metabolism characterized by reduced activity of serum and tissue alkaline phosphatase, abnormal mineralization of bone, and phosphoethanolaminuria. Clinically it occurs in a severe infantile form and a more benign childhood and adult form. The inheritance pattern has been consistent with an autosomal recessive gene substitution, the homozygotes presenting with the frank disease and the heterozygotes manifesting some of the findings, *i.e.* low or borderline alkaline phosphatase and/or phosphoethanolaminuria.

A study of a family is presented in which a father and two sons had the frank disease; the mother and two siblings did not have the disease and did not demonstrate any of the stigmata of the heterozygote.

From this finding the presence of a single autosomal dominant substitution or even the possibility of more than one mode of inheritance in hypophosphatasia is postulated.

The precise genetic mechanism of hypophosphatasia is as yet unresolved.—*William C. McCarty, Jr., M.D.*

Richardson, James A., Jr., and Diddams, Albert C. Maffucci's syndrome. *A.M.A. Arch. Int. Med.*, Feb., 1962, *109*, 186–191. (Address: Public Health Service, Department of Health, Education, and Welfare, 210 State Street, New Orleans 18, La.)

Maffucci's syndrome consists of dyschondroplasia, multiple cavernous venous hemangiomata, and phlebectasia. Forty three cases have been reported in the literature. There is an increased incidence of malignancy, especially sarcomata.

The authors report a patient with severe venous changes and resultant circulatory disturbances. The patient was a 22 year old white male, admitted for venous stripping. He had had asymmetry of his limbs since birth, the left side being smaller than the right. He had a 2 year history of difficulty with prolapsing hemorrhoids. He had prominent veins and varicosities dating from about age 18. He experienced transient giddiness and visual blurring on assuming an erect position. He could not stand perfectly still for more than a few seconds without feeling vaguely uncomfortable. He relieved this by moving. He had been in good health, with normal energy and above average intelligence.

His father had varicose veins; his mother was afflicted with chronic arthritis.

His blood pressure when sitting varied from 65/40 to 95/40 mm. of Hg with a pulse of 60. The supine blood pressure was 100/50. On standing his blood pressure fell to 40/0, and the pulse rose to 120/min. This persisted until exercise was begun. Wrapping the legs with bandages helped support the blood pressure slightly. Although the left extremities were shorter, there was no apparent difference in bony structure or muscle strength. Blood volume (Evans blue) was 7,500, his estimated normal being 4,000 ml. A decholin circulation time was unobtainable. The electrocardiogram was normal. There were no esophageal varices. The deep veins of the leg as well as the pelvic veins were dilated on the venogram.

A bilateral stripping and ligation were done. This did not help the standing blood pressure pattern. Elastic stockings were advised and he was discharged. The pathologists detected no abnormality of the stripped veins.

The authors feel that this entity is not caused by congenital venous valve absence, but rather exhibits a vague basic cause of phlebectasia. They believe that there may be a hereditary influence. This patient's dyschondroplasia affected mainly the growing ends of the long bones.

The opinion is expressed that this entity is more common than the reports indicate—*Delano Z. Arvin, M.D.*

Ariel, Irving M., and Jacobs, Paul A. Extraosseous chondrosarcoma arising from the tendon Achilles. *Bull. Hosp. Joint Dis.*, Oct., 1961, *22*, 129–136. (From: The Soft Somatic Tissue Tumor Service, Hospital for Joint Diseases, New York, N. Y.)

One case of proven chondrosarcoma arising in the Achilles tendon is reported. The original tumor was resected eleven years previous to the final amputation of the leg.

Theories concerning the etiology of extraskeletal chondroblastic tumors are introduced. A review of reported instances of osteoblastic and chondroblastic tumors arising in soft tissues is included. The degree of malignancy and the treatment of these tumors is considered.—*David C. Alftine, M.D.*

Haider, Riaz, and Storey, Geoffrey. Spontaneous fractures in rheumatoid arthritis. *Brit. M. J.*, June, 1962, *2*, 1514–1516. (Address: Bethnal Green Hospital, London, England.)

In the authors' review of the literature, spontaneous fractures in rheumatoid arthritis are said to be rare, apart from those incidental to steroid therapy. They report 5 cases of this occurrence in females from 62 to 70 years of age, none of whom had received steroid therapy. All were typical rheumatoid arthritics and fulfilled the criteria necessary for a definite diagnosis. Four of these patients sustained a fracture of the hip—in one case, bilateral—following no known trauma. The fifth patient had a fracture through the right lower fibula; one year later she was found to have fractures of the left lower fibula and tibia resulting from a slight stumble.

In this latter case and the one with bilateral hip fractures, there was felt to be roentgen evidence of a gradual development of these fractures—referred

to as "dormant" by Fineschi. There may be a locally painful stage without roentgenographic interruption of bone. Later, callus may make the fracture line obvious, but it may still be incomplete. In Fineschi's series, which was mainly comprised of metatarsal fractures, little or no displacement was the rule.

The cause is obscure. There may be no change in bone density in the area of the fracture. Though no gross abnormality of calcium metabolism was present in these patients, one revealed laboratory findings of slight osteoporosis of the senile type. This, in combination with the age and sex of these patients, is probably a factor in production of spontaneous fractures. Steroids may aggravate these factors.—*William H. Baker, M.D.*

ZVAIFLER, NATHAN J. Chronic postrheumatic fever (Jaccoud's) arthritis. *New England J. Med.*, July, 1962, *267*, 10–14. (From: The Department of Medicine, Division of Metabolism and Arthritis, Georgetown University Hospital, Washington, D. C.)

Various explanations for the co-existence of chronic deforming arthritis and valvular heart disease in a patient have been proposed, one of which is known as Jaccoud's arthritis or chronic postrheumatic arthritis in which rheumatic fever itself is thought to produce chronic joint deformity.

Two cases are presented (a 26 year old male and a 37 year old female) both of whom suffered very severe prolonged attacks of acute rheumatic carditis at an early age. After recovery from the acute stage, neither patient complained of joint symptoms. However, each gradually developed typical ulnar deviation of the fingers and subluxation of the metacarpophalangeal joints. There was no evidence of bone erosion or joint inflammation, the sedimentation rate was normal, and routine tests for the rheumatoid factor were negative.

Other studies on this condition are referred to, and a list of 7 characteristics of the syndrome suggested by E. G. L. Bywaters is included—*Richard Van Buskirk, M.D.*

VESPIGNANI, L., VENTURINI, G., and ACERBONI, S. Reperti artrografici e clinici nelle disinserzioni e nelle lassitá meniscali. (Arthrographic and clinical findings in disinsertion and laxity of the menisci.) *Radiol. med.*, Mar., 1962, *48*, 209–221. (Address: Dott. Prof. Luigi Vespignani, Dorsoduro 187, S. Gregorio-Venezia, Italy.)

The traumatic lesions of the menisci of the knee are rupture, disinsertion and dislocation. Another lesion which is still under discussion is the so-called "laxity of the meniscus."

In capsular disinsertion, the meniscus is ruptured at the point of attachment to the joint capsule. The authors divide the disinsertion into complete or partial, in a vertical direction; or total or segmental, in a horizontal direction.

The roentgen findings are well known and have been described by Lindblom and Ficat in their monographs on arthrography of the knee. Of a certain interest in this article are the roentgen findings noted in arthrographic studies of patients with a laxity of the insertions of menisci to the joint capsule. This results usually in an abnormal mobility of the meniscus causing a recurrent dislocation of the meniscus itself; without, however, permanent block of the knee.

In a series of 22 cases operated on in the Department of Orthopedics and Traumatology of the Ospedali Civili Riuniti of Venice, the histories show in most cases an old trauma, repeated effusions although not severe, and "snapping knees." The roentgen findings, in the routine arthrograms, are very frequently negative. However, in the fourth position of Lindblom, the medial meniscus is visualized in practically all the cases as a long and flat triangle appearing almost as a discoid. This finding is considered by the authors to be pathognomonic.—*A. F. Govoni, M.D.*

JACOBS, PHILIP. Reversible ectopic soft tissue ossification following measles encephalomyelitis. *Arch. Dis. Childhood*, Feb., 1962, *37*, 90–92. (From: The Royal Orthopaedic Hospital, Birmingham, England.)

Paraplegia in childhood is a relatively uncommon condition and there are few reports of soft tissue ossification accompanying paraplegia in childhood.

The author reports a case of ectopic ossification around the hips following paraplegia secondary to measles encephalomyelitis. This is the first known report of this condition arising as a complication of measles. Large hood-like plaques of new bones were seen on both sides, on the right side extending from the anterior inferior iliac spine to the femoral neck anteriorly. Slender bridges of new bone extended from the ischium to the lesser trochanter on either side.

Almost complete resorption of the ectopic bone occurred following conservative measures. If recovery from paraplegia is possible, the laying down of new bone appears to be reversible.—*William J. Miller, M.D.*



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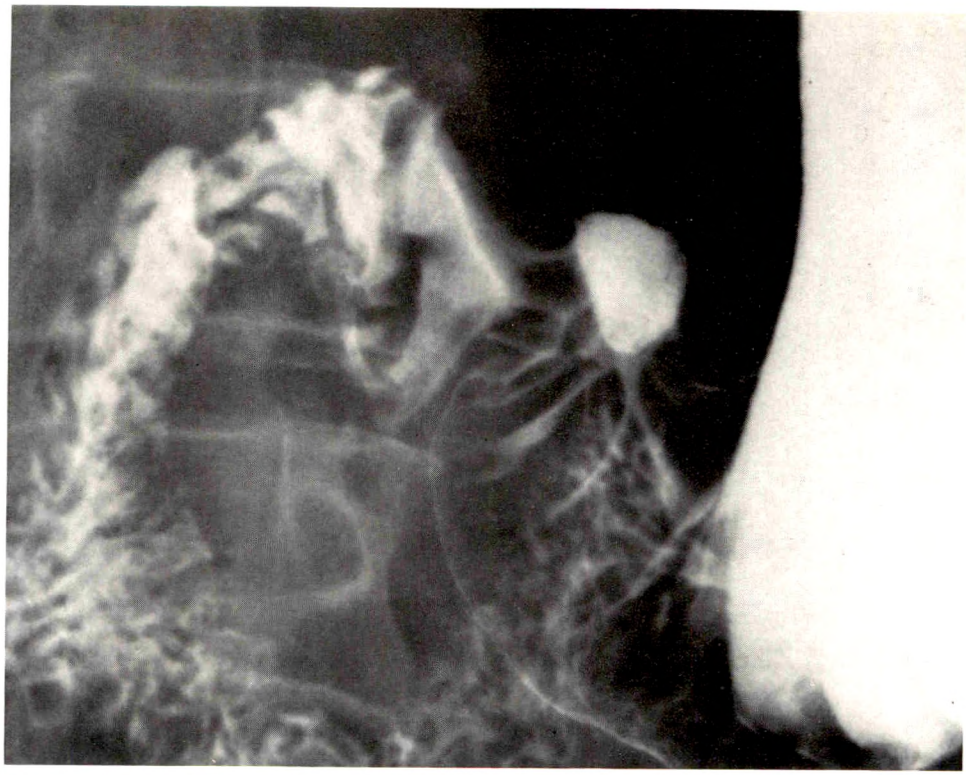


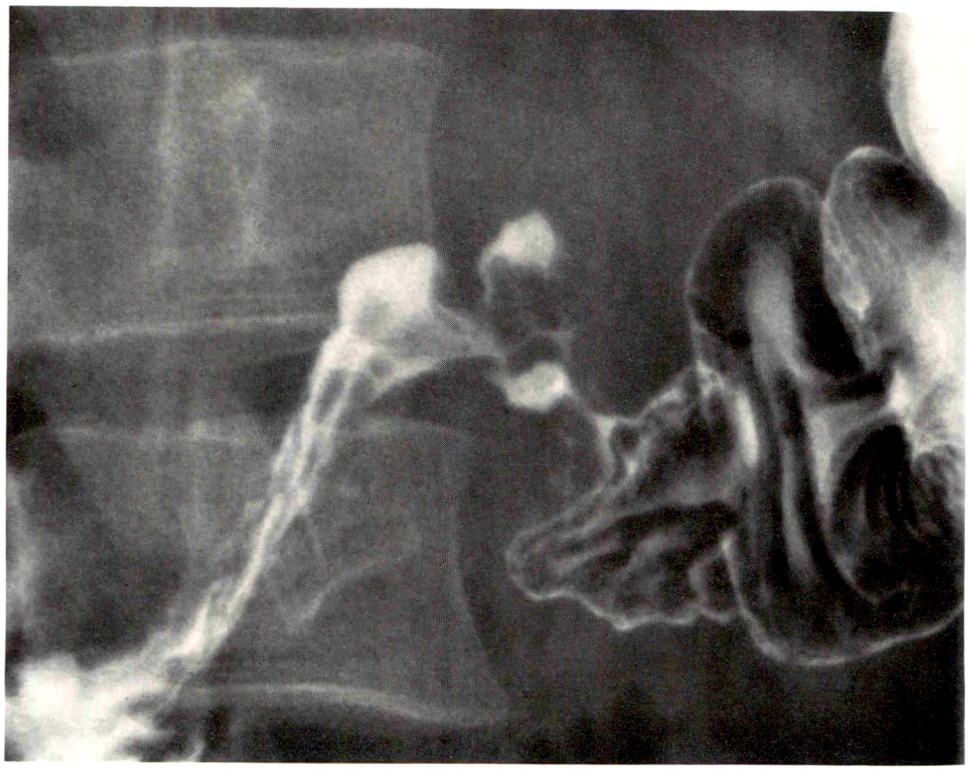
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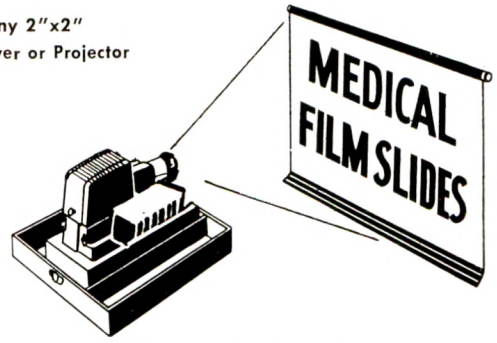
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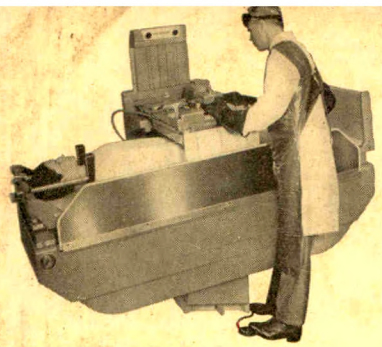
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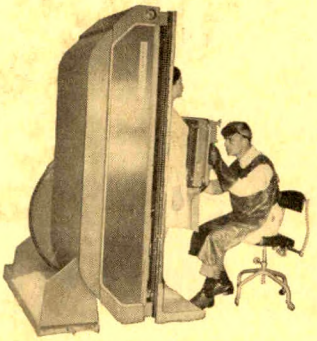
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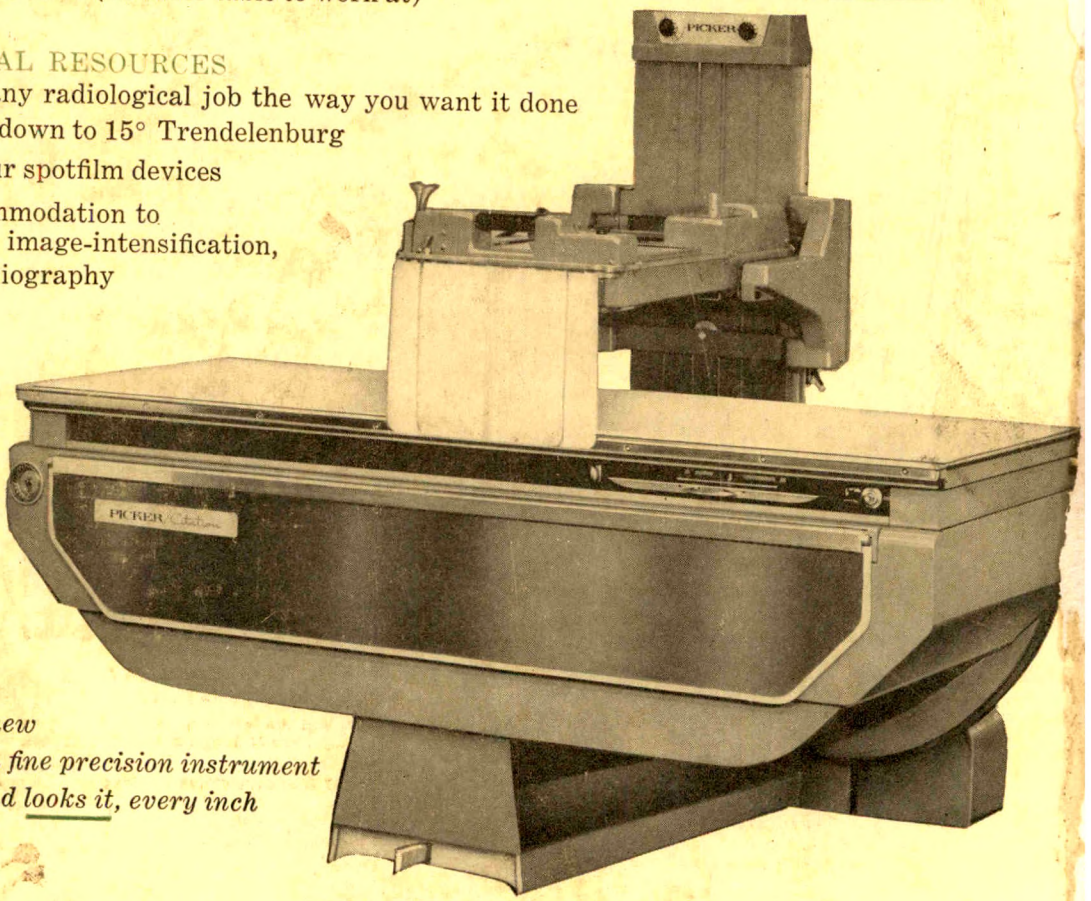
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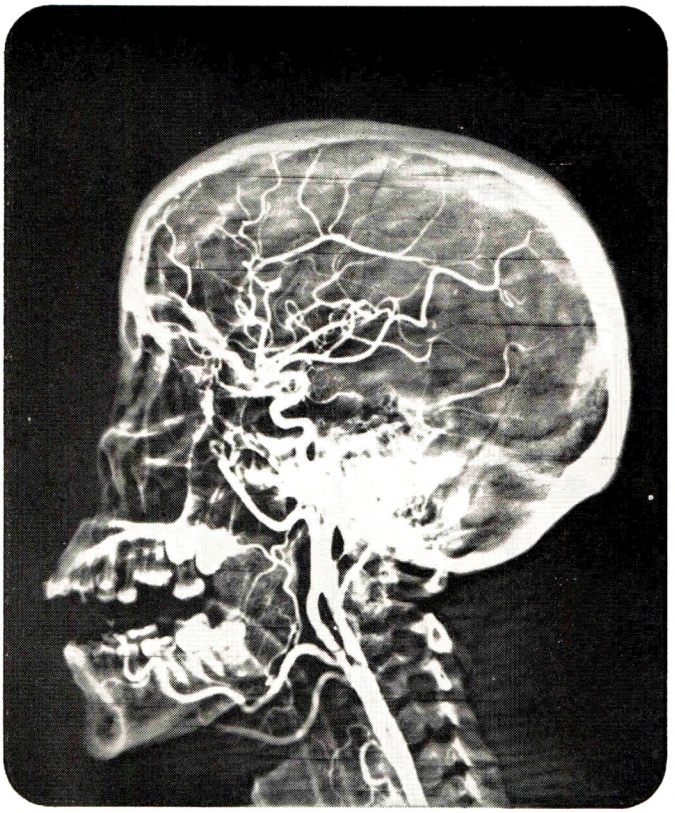
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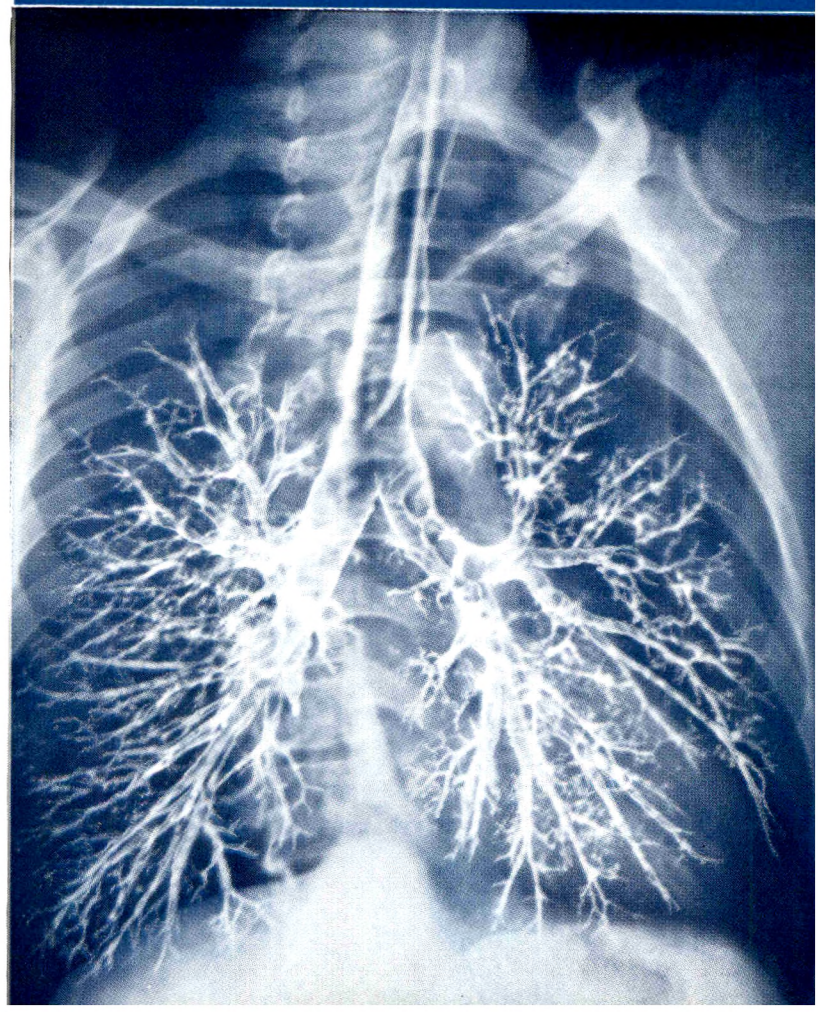
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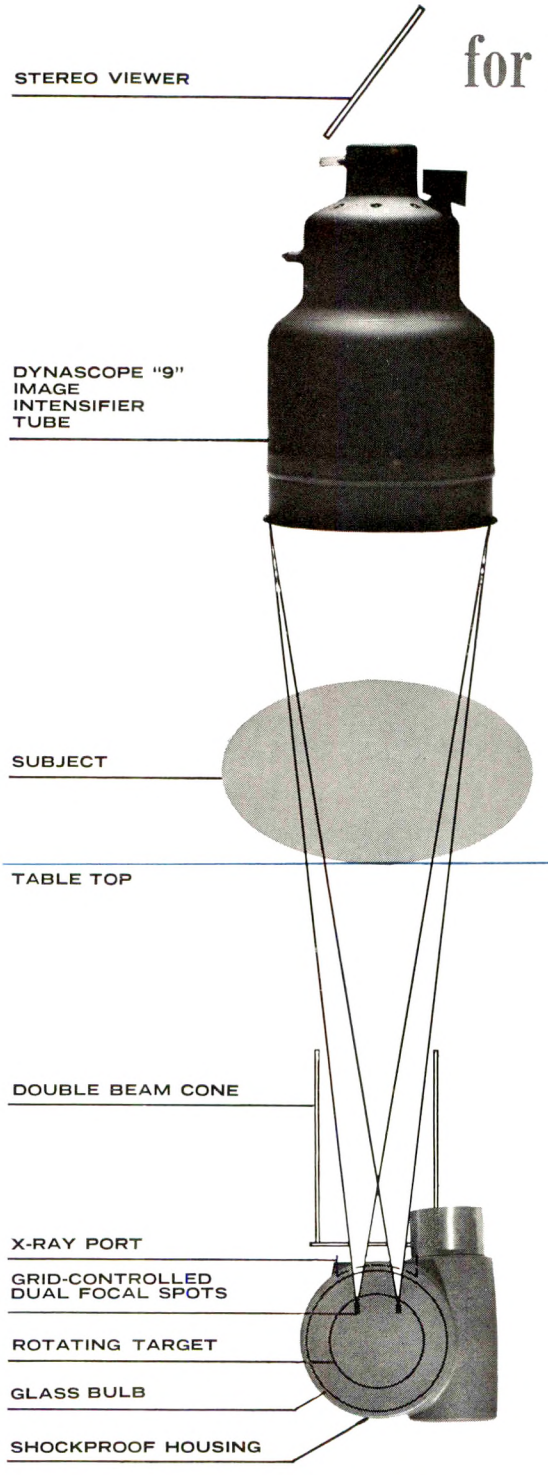
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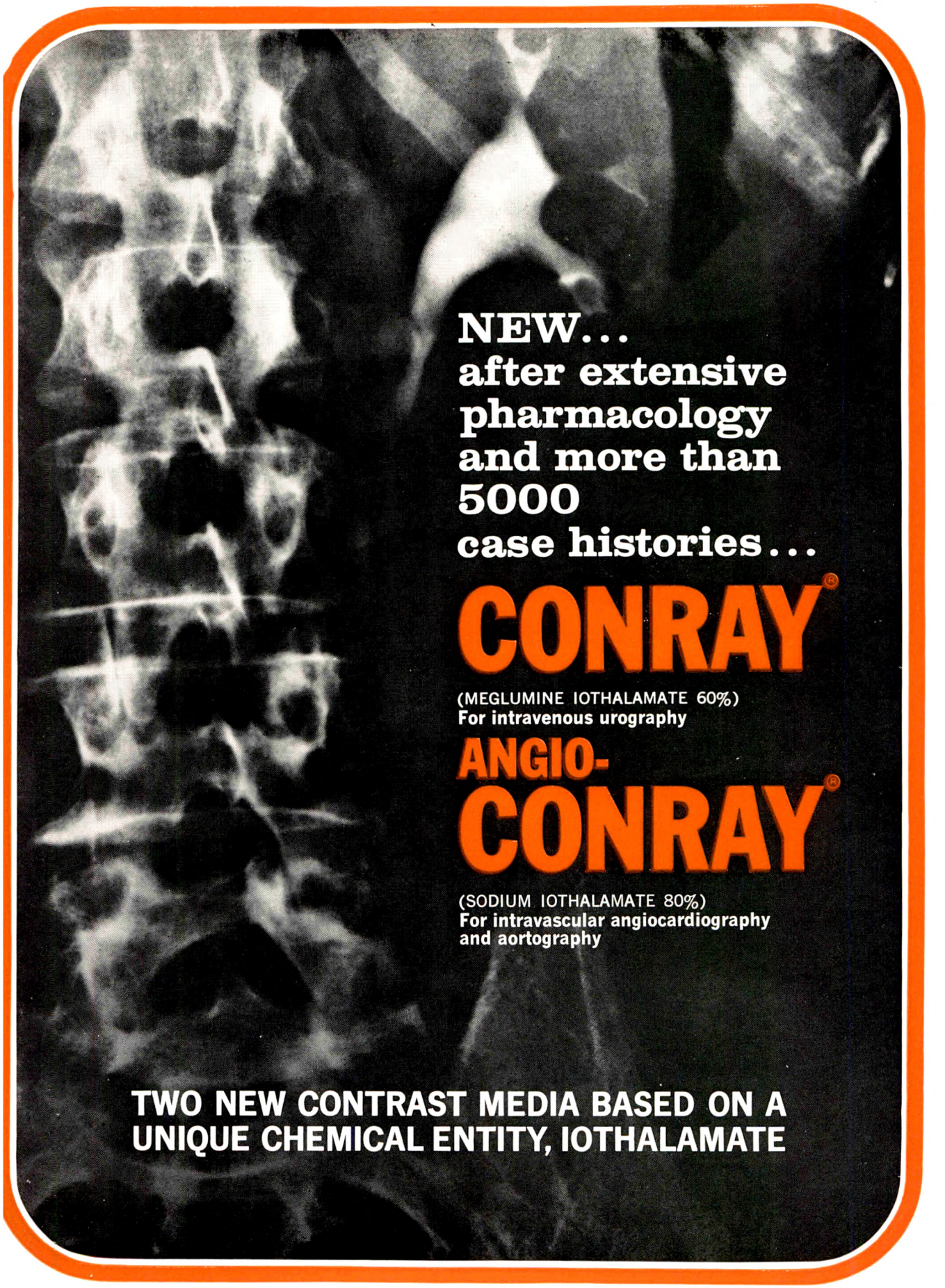
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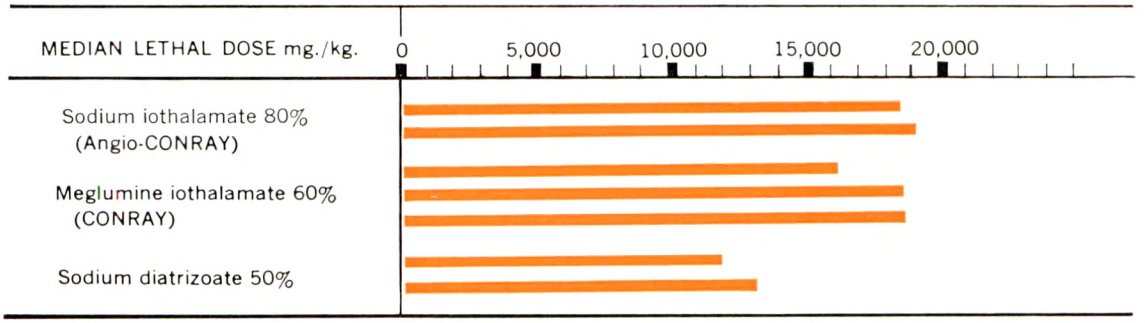
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Pharmacological findings: (cont'd)

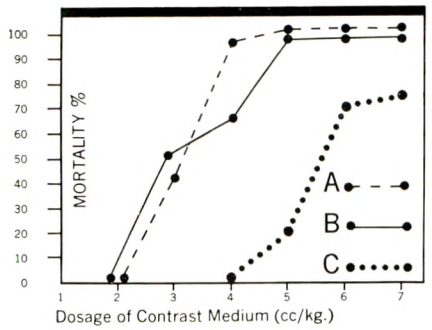
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"Thus the margin of safety in intravenous injections was far greater with Angio-CONRAY." [2]

BLOOD BRAIN BARRIER STUDIES IN DOGS[9,14]

Using a modification of previously reported blood brain barrier tests (Broman and Olsson; Whiteleather; De Saussure), intracarotid injections were made in dogs using 25 cc. of meglumine iothalamate 60% and sodium diatrizoate 50% followed by infusion of Trypan blue dye.

	No. of Dogs	None	Barely Perceptible	Faint	Distinct	Intense
25 cc. meglumine iothalamate 60% (CONRAY)	14	4	3	6	1	0
25 cc. sodium diatrizoate 50%	11	0	0	2	3	6

Even more important than brain staining were the differences in neurological responses when the two media were injected. Dogs receiving sodium diatrizoate (11 dogs) exhibited numerous observable neurological responses such as strong contractions of the neck and thoracic muscles (7 dogs), clonicotonic convulsions and hypersensitivity to sound and touch (9 dogs).

Dogs receiving CONRAY exhibited no convulsions nor hypersensitivity to sound and touch. Four showed slight to mild contractions of the neck and thoracic muscles. The remaining 10 dogs appeared unaffected by the injections.

Clinical commentary:

IN OVER 5000 CASES, [1-3, 6, 7, 12-14, 16, 17]

there has been general agreement among investigators that patient tolerance with iothalamate has been better than that previously experienced with other available agents.

"...The intravenous injection of /CONRAY/ for urography is practically devoid of unpleasant reaction." **STEINBERG, I. and EVANS, J. A.**[16]

"In view of its several distinct advantages, it is likely that iothalamate will supersede presently available agents for cardiovascular contrast visualization." **STRAUBE, K. R. and DOTTER, C. T.**[17]

"At the present time, Angio-CONRAY would appear to be the concentrated angiographic medium of choice." Foster, et al. further state that "experimental studies clearly demonstrated that sodium iothalamate is the least toxic angiographic contrast medium yet tested." **FOSTER, J. H., et al.**[2, 3]

"If further clinical experience confirms our impression of its relative safety and freedom from side effects, /iothalamate/ will, in fact, warrant the term 'drug of choice'—at least until a better preparation is found." Citing the importance of the need for rapid delivery of concentrated contrast media through small bore catheters, Dotter, et al. further observed that "...from this point of view, /iothalamate/ is an outstanding medium." **DOTTER, C. T., et al.**[1]

"Clinical experience with a new concentrated contrast agent, Angio-CONRAY, in angiocardiography, nephrotomography, intravenous aortography, and retrograde renal arteriography indicates that the usual reaction was mild and transient, and was well tolerated. Low viscosity and ready solubility of Angio-CONRAY permit ease and speed of injection. These factors, together with good contrast visualization, make Angio-CONRAY a preferable contrast medium for angiographic procedures." **KANICK, V. and FINBY, N.**[7]

"Angio-CONRAY is the agent of choice for aortography and angiocardiography. CONRAY is the preferred agent for intravenous urography... It appears that the compound is more rapidly excreted than the other common opaques and maximum density of contrast is evident in five minutes." **MARSHALL, M. D. and LING, J. T.**[13]

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1. Dotter, C. T.; Straube, K. R.; Bilbao, M. K., and Hinck, V. C.: New Contrast Medium for Intravascular Use, Northwest Med. *61*:41-6 (Jan.) 1962. 2. Foster, J. H.; Sessions, R. T.; Winfrey, E. W.; Killen, D. A., and Collins, H. A.: Clinical and Experimental Evaluation of Angiographic Contrast Media, Scientific Exhibit presented at the 111th Annual Meeting of the American Medical Association, Chicago, Illinois, June, 1962. 3. Foster, J. H.; Winfrey, E. W.; Killen, D. A., and Sessions, R. T.: A New and Superior Angiographic Contrast Medium, Sodium Iothalamate 80%: A Clinical and Experimental Evaluation. To be published. 4. Bernstein, E. F.; Mackey, G. C.; Emmings, F. G., and Amplatz, K.: Experimental Evaluation of Renal and Spinal Cord Tolerance to a New Angiographic Agent, Angio-CONRAY, Surgery *51*:663-7 (May) 1962. 5. Bernstein, E. F.; Reller, C. R., and Grage, T. B.: Experimental Studies of Angio-CONRAY: A New Angiographic Agent, Radiology. To be published. 6. Dotter, C. T.; Straube, K. R.; Bilbao, M. K., and Hinck, V. C.: An Initial Report on Iothalamate. A New Contrast Agent for Intravascular Administration, Scientific Exhibit presented at the Annual Meeting of the Radiological Society of North America, Chicago, Illinois, November, 1961. 7. Kanick, V., and Finby, N.: Angio-CONRAY: A New Angiographic Contrast Agent. To be published. 8. Killen, D. A.; Foster, J. H., and Scott, H.W., Jr.: Toxic Reactions Incident to Urokon Aortography as Related to the Volume of Contrast Medium Injected. Addendum.

Physical characteristics:

Iothalamate is a new chemical entity synthesized and developed by Mallinckrodt Pharmaceuticals. It is chemically identified as 5-acetamido-2, 4, 6-triiodo-N-methylisophthalamate. CONRAY is an aqueous solution of meglumine iothalamate at 60% concentration. Angio-CONRAY is an aqueous solution of sodium iothalamate at 80% concentration.

Both in iodine content and viscosity, Angio-CONRAY is superior to comparable diatrizoates. It has the highest iodine content (48%) of any available contrast medium, and its viscosity is almost 3 times lower than comparable diatrizoates.



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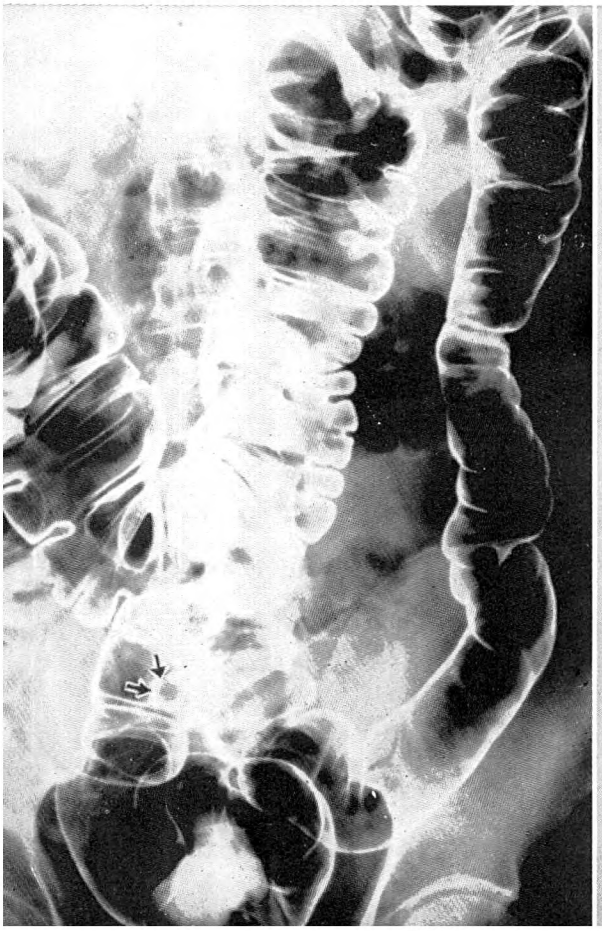
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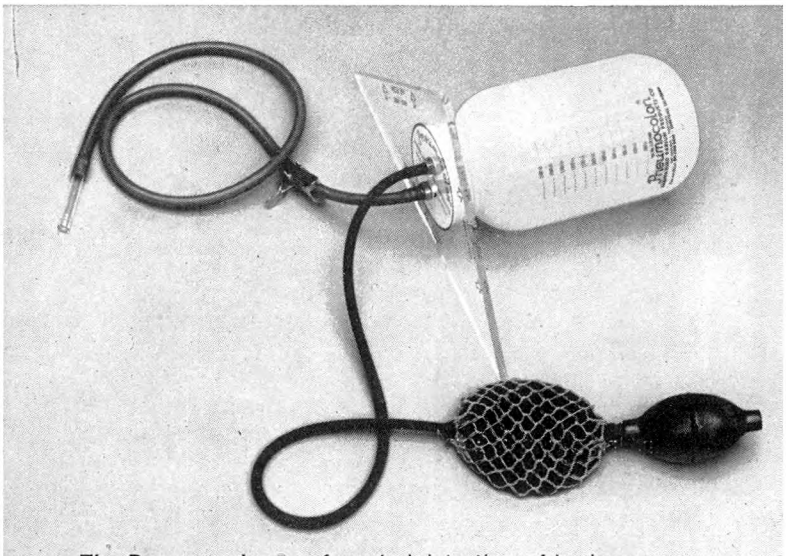
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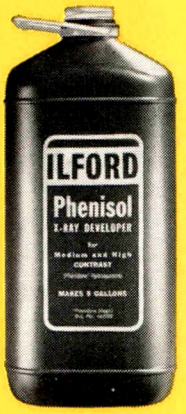
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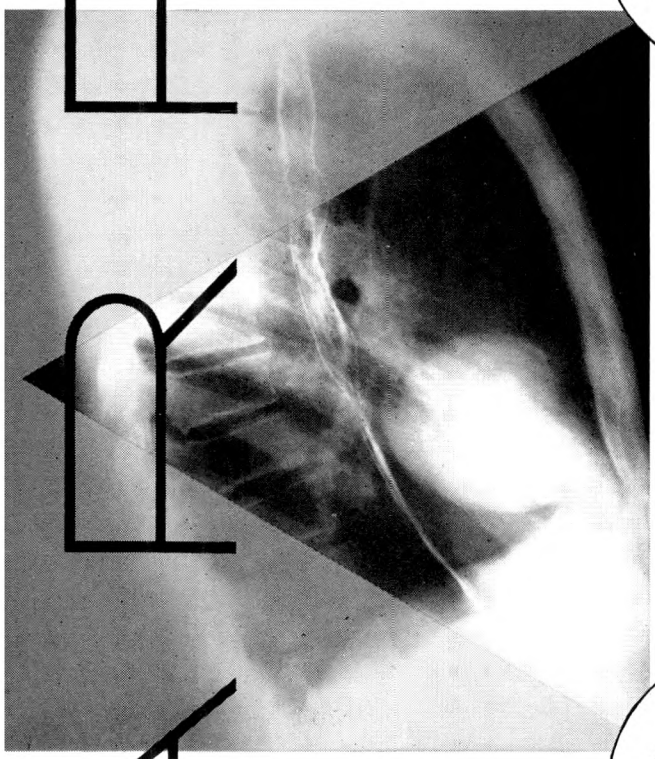
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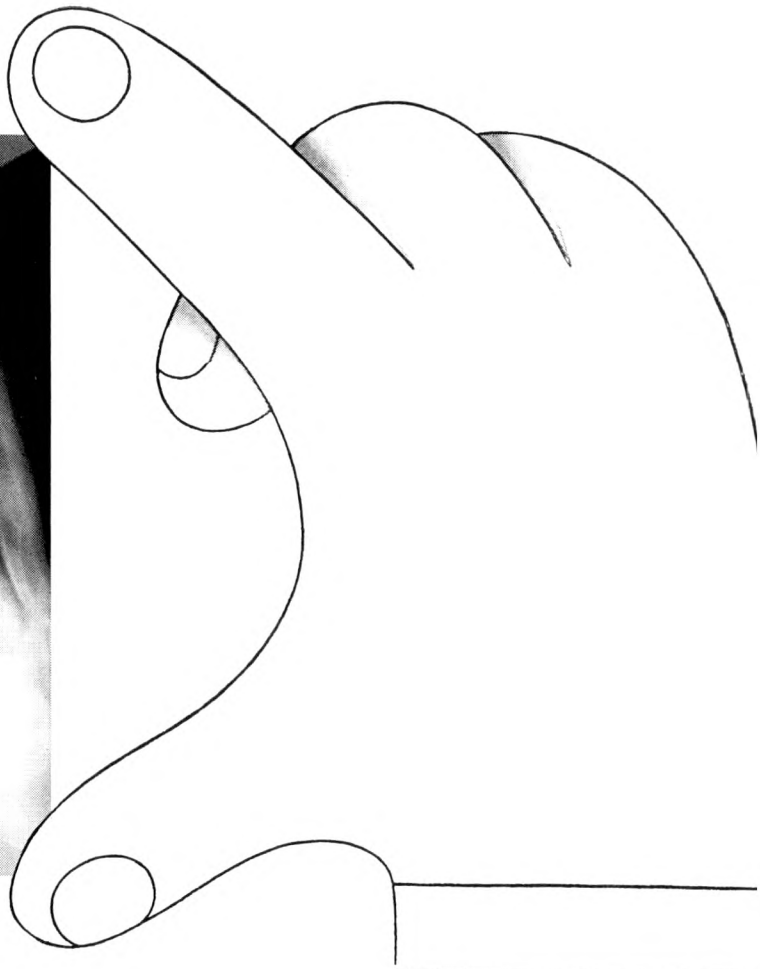
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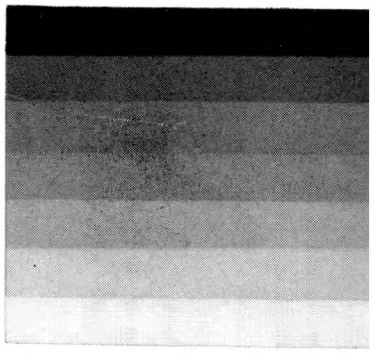
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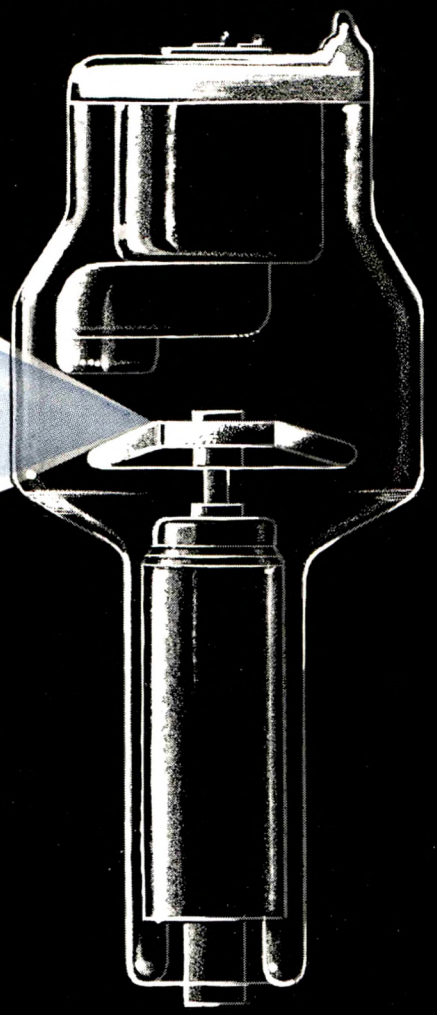
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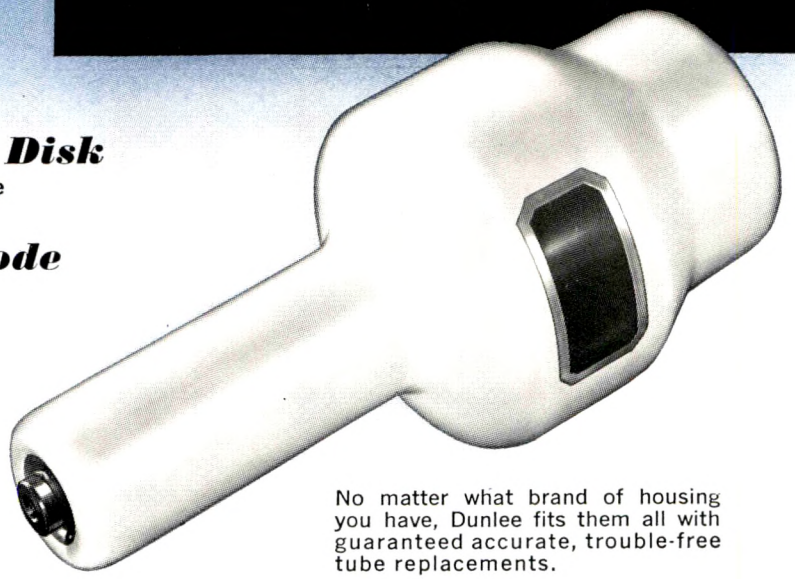
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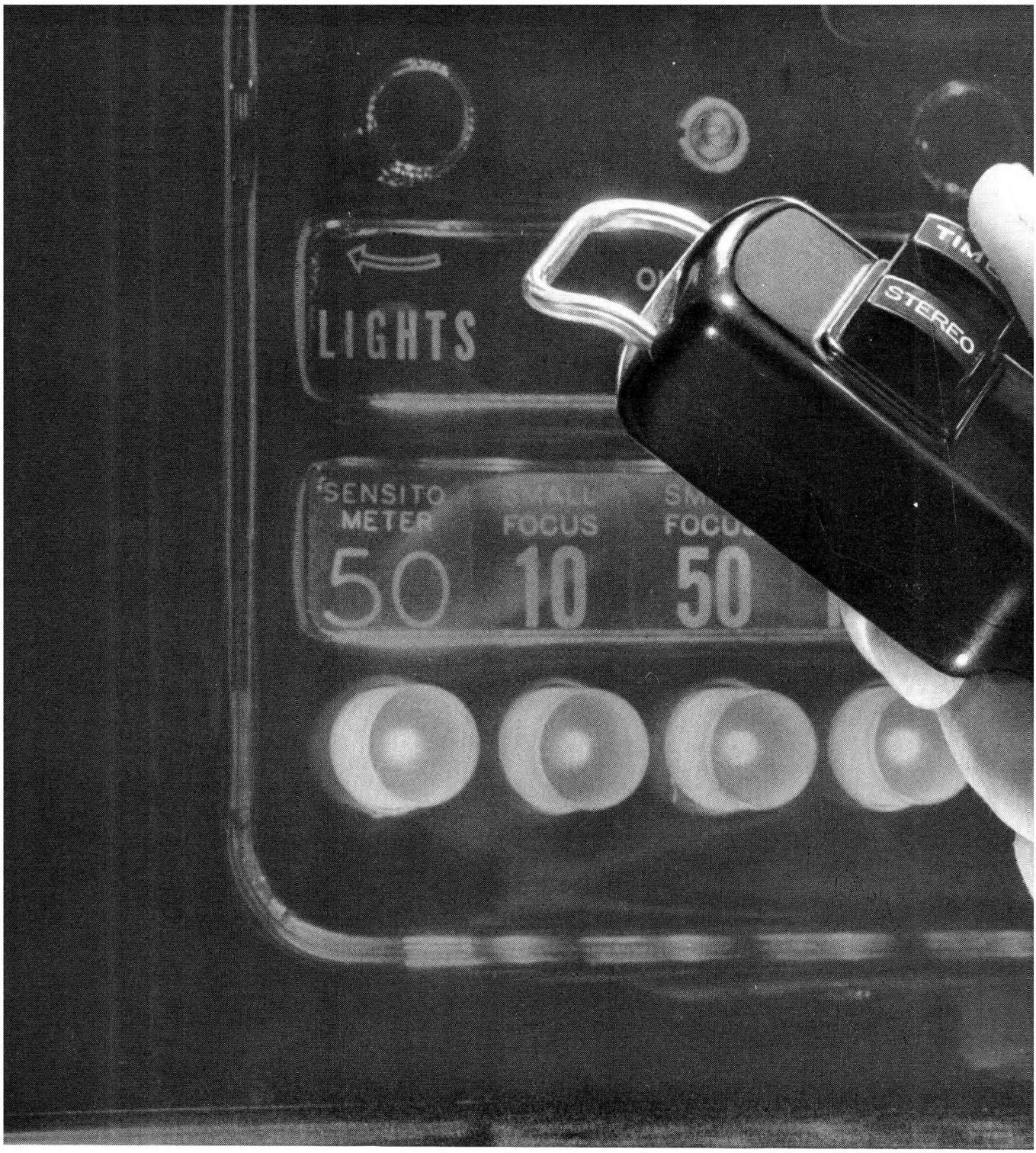
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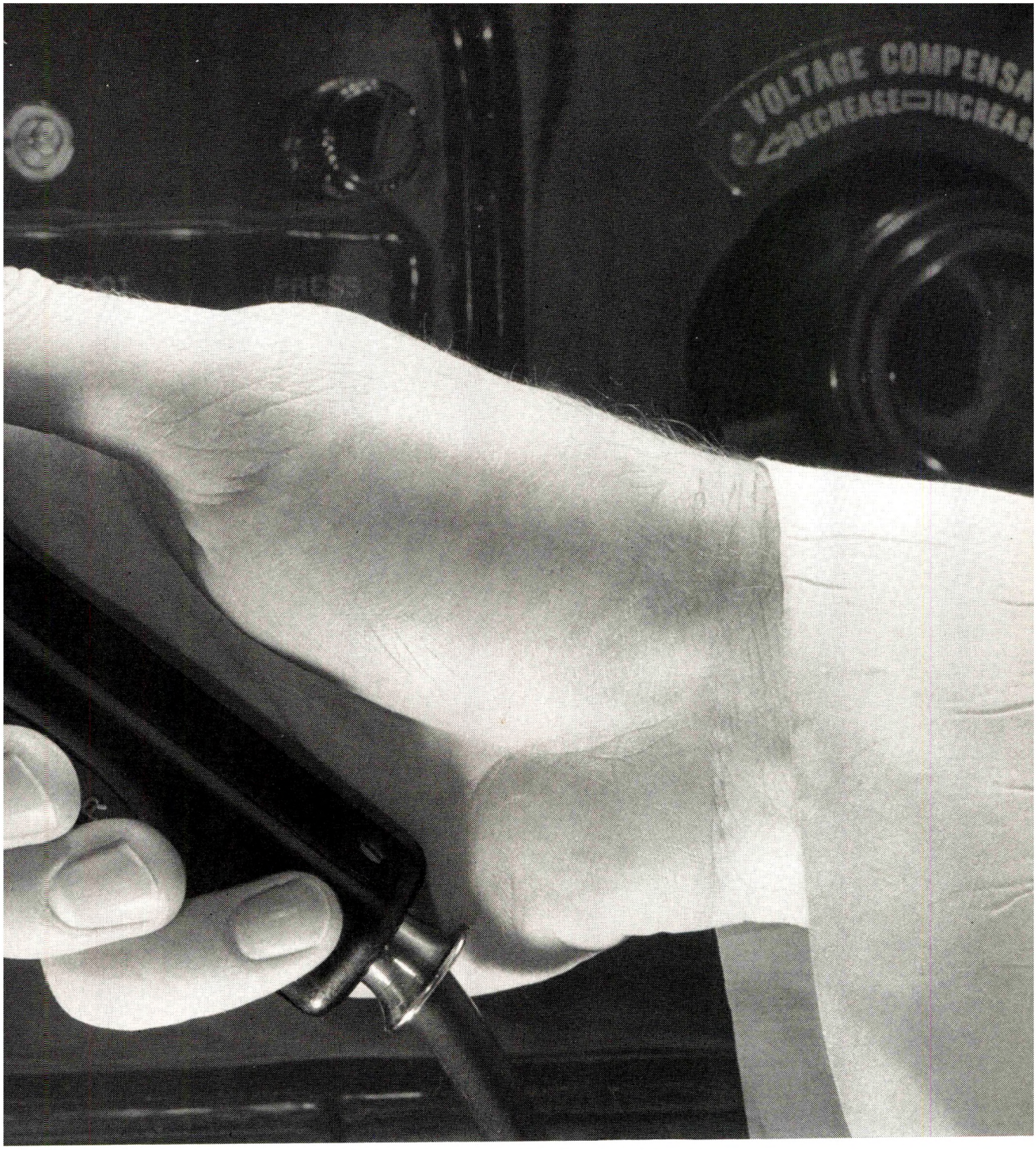
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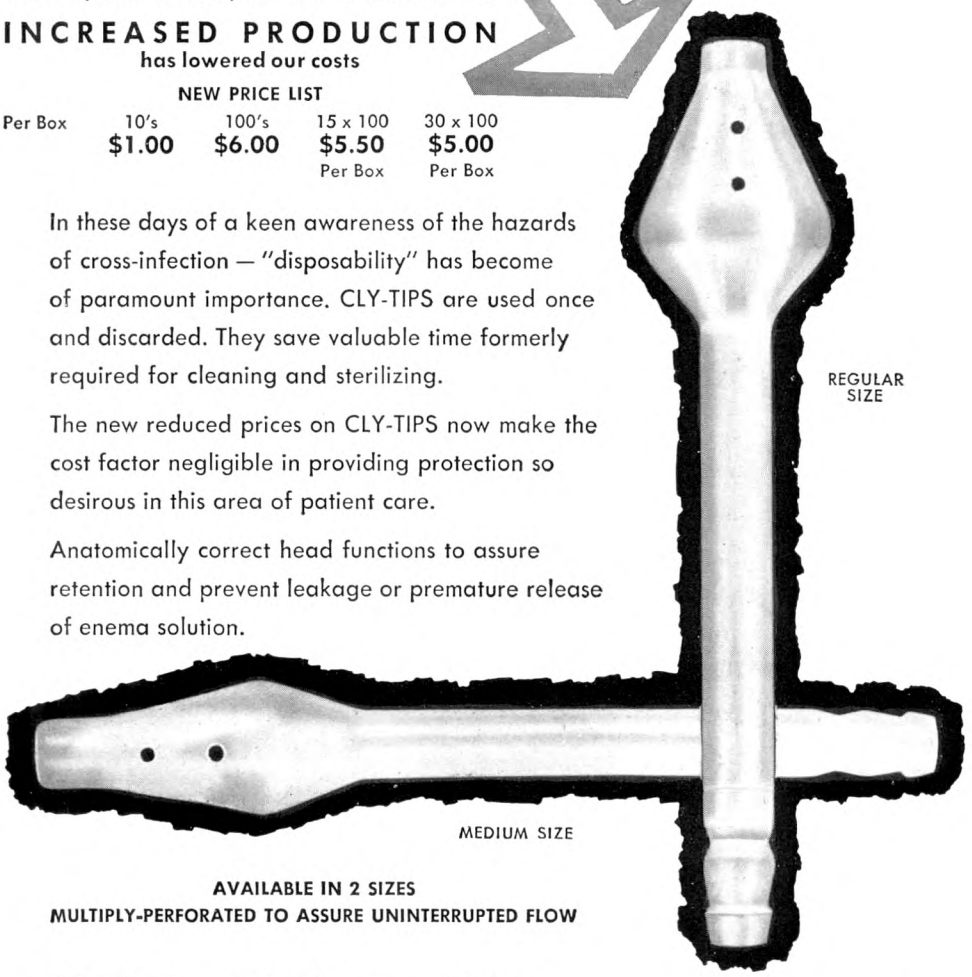
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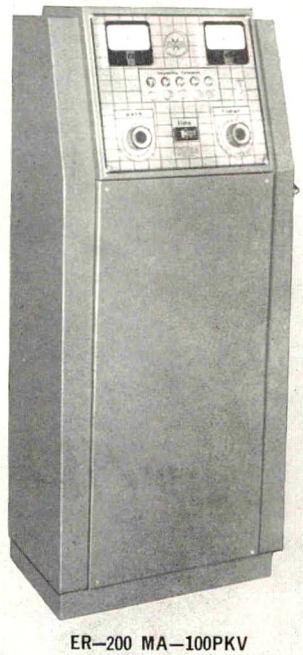
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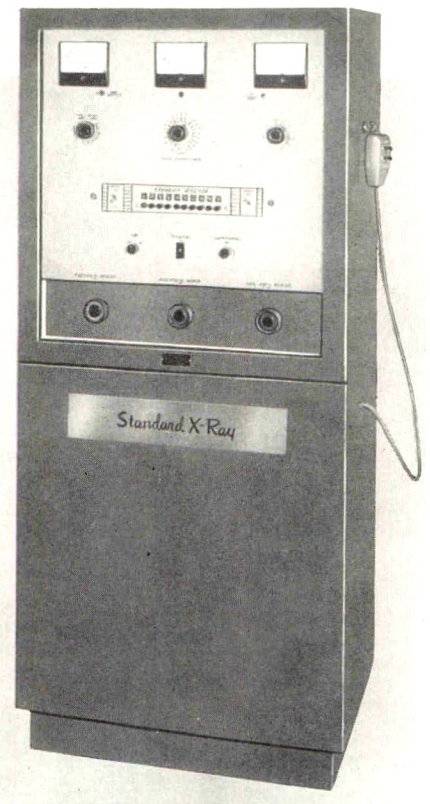
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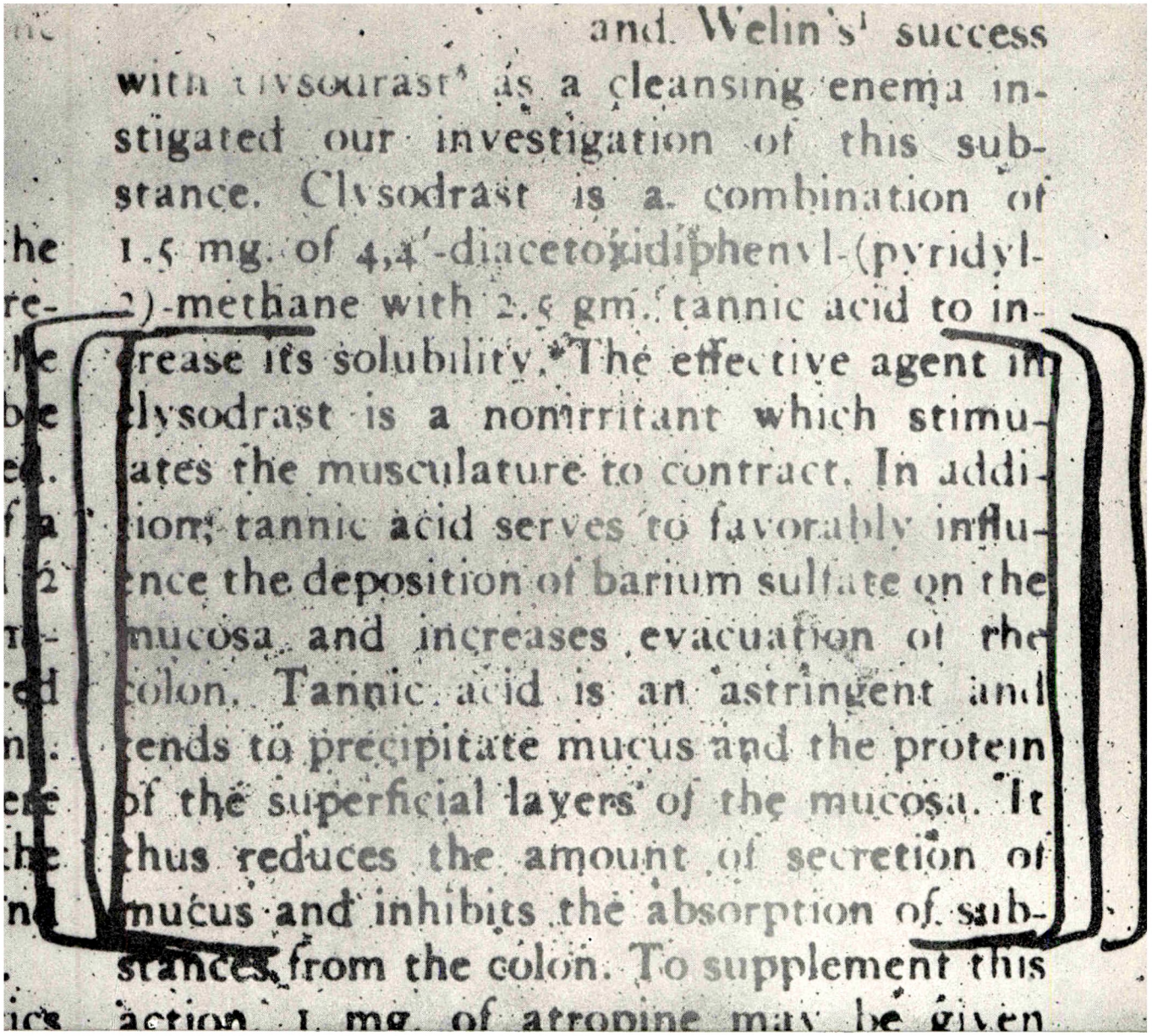
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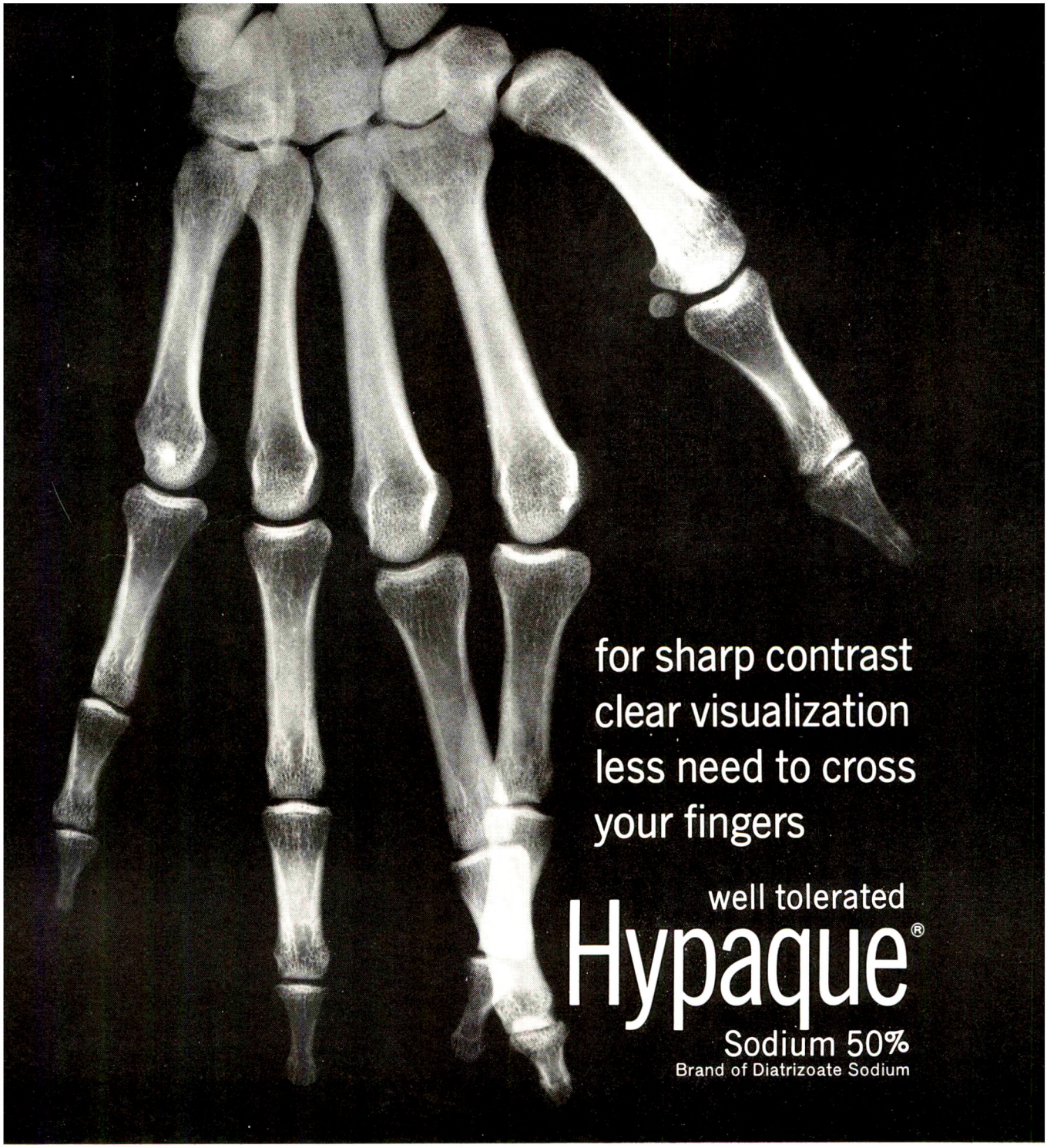
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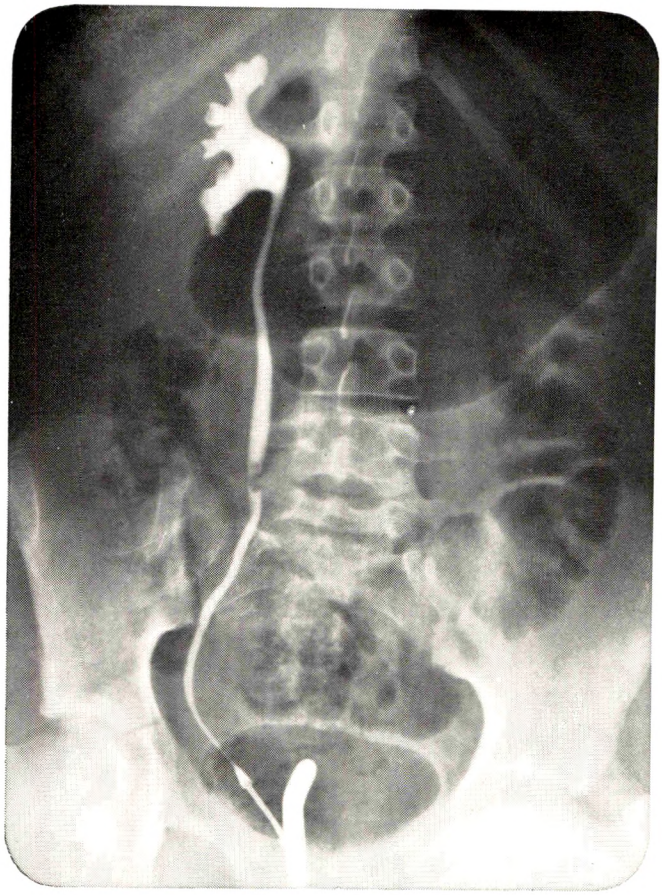
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2. Keogh, R.K., and Fraser, R.G.: J.A. Canad. Radiol. 9:66, 1958.
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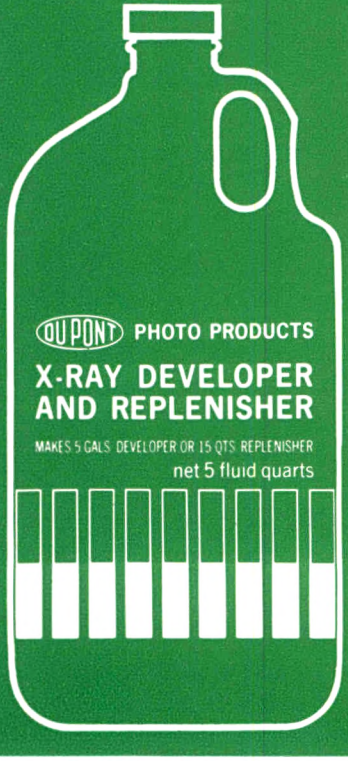
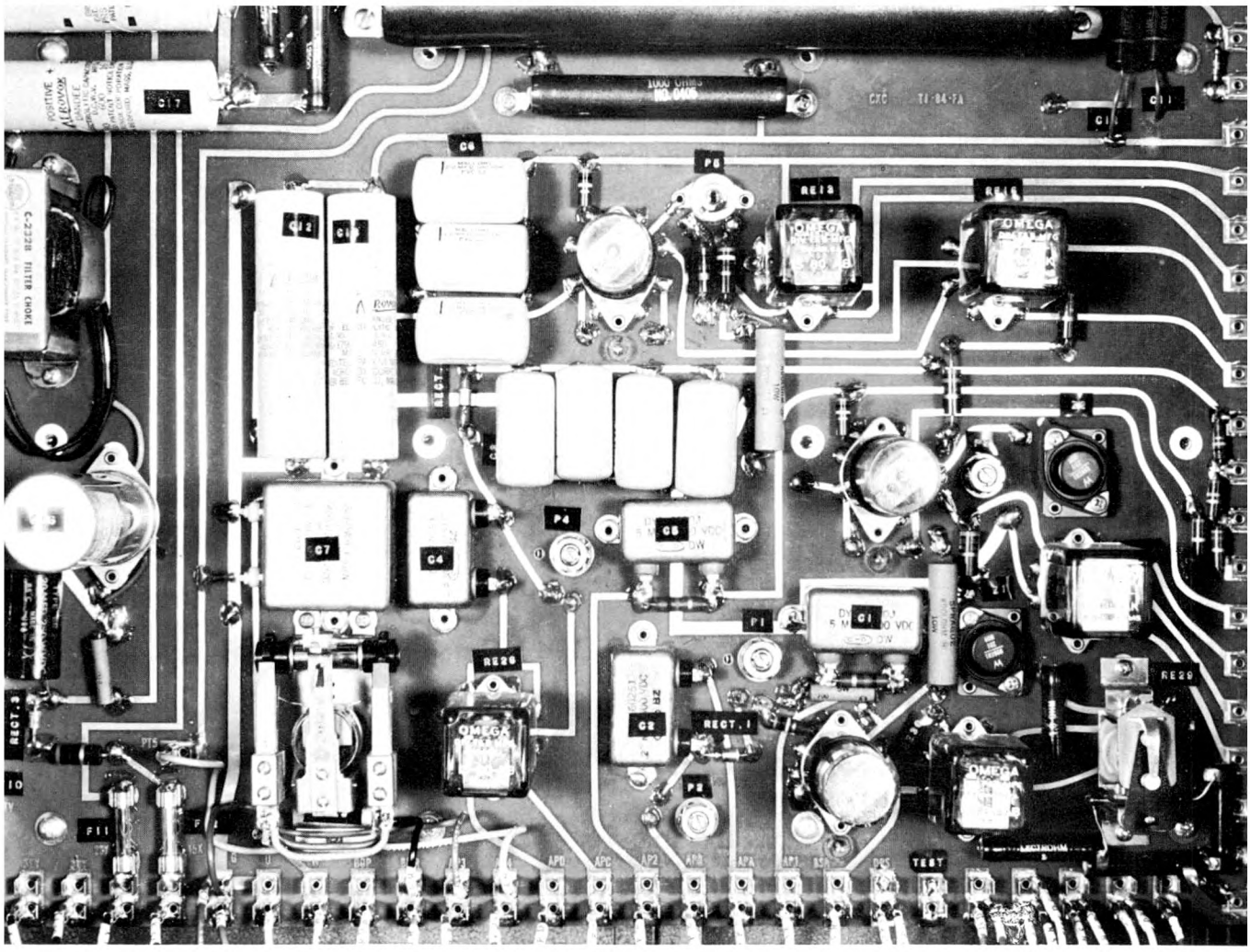


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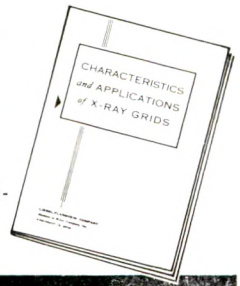
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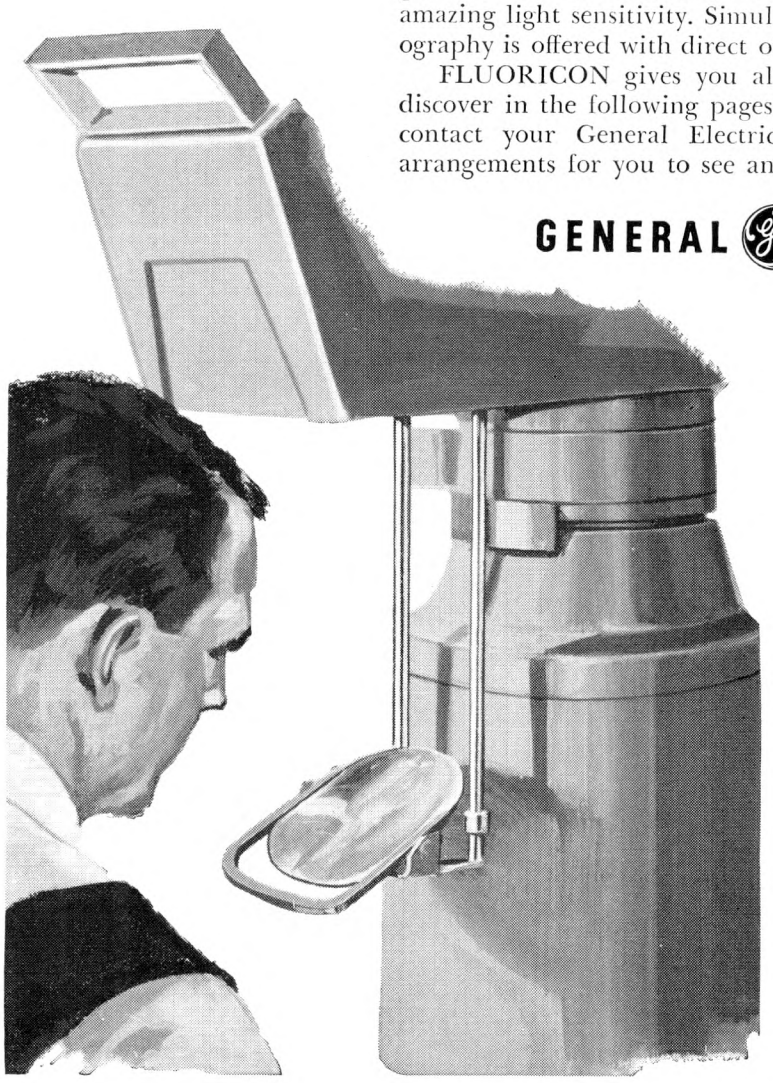
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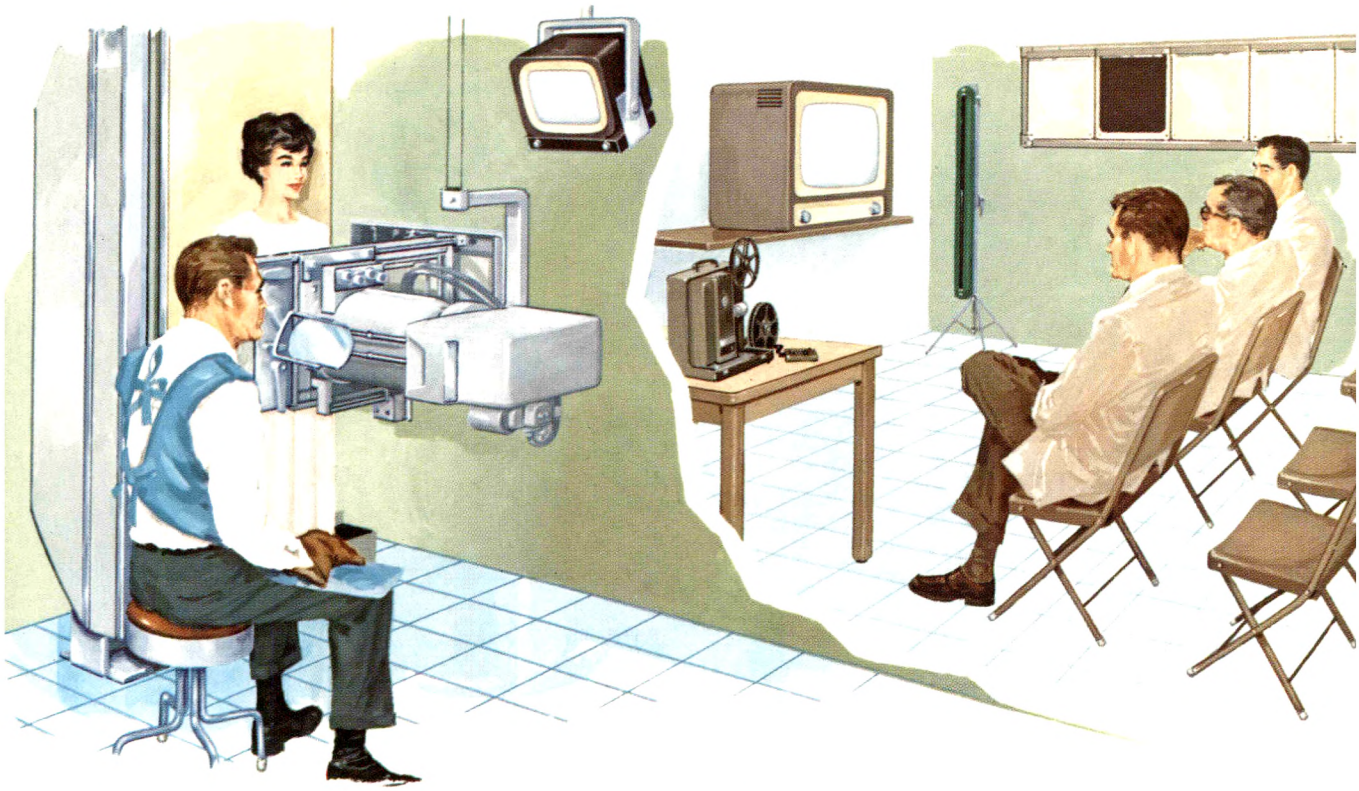
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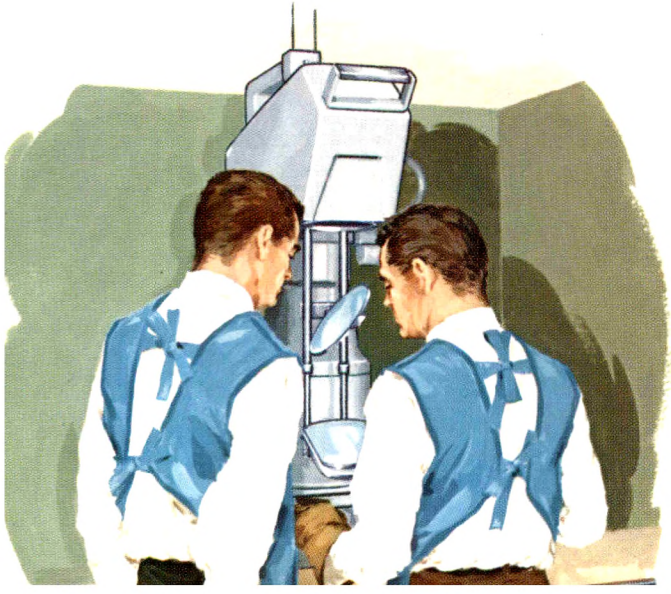


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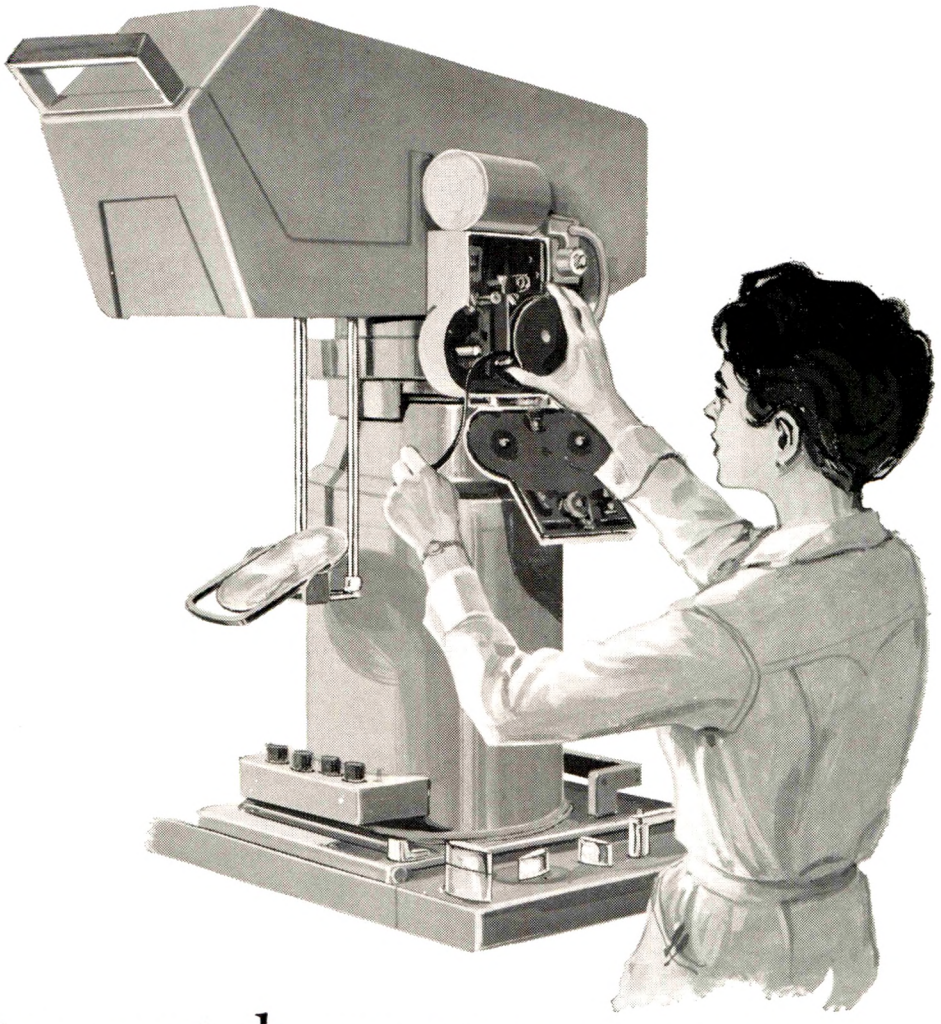
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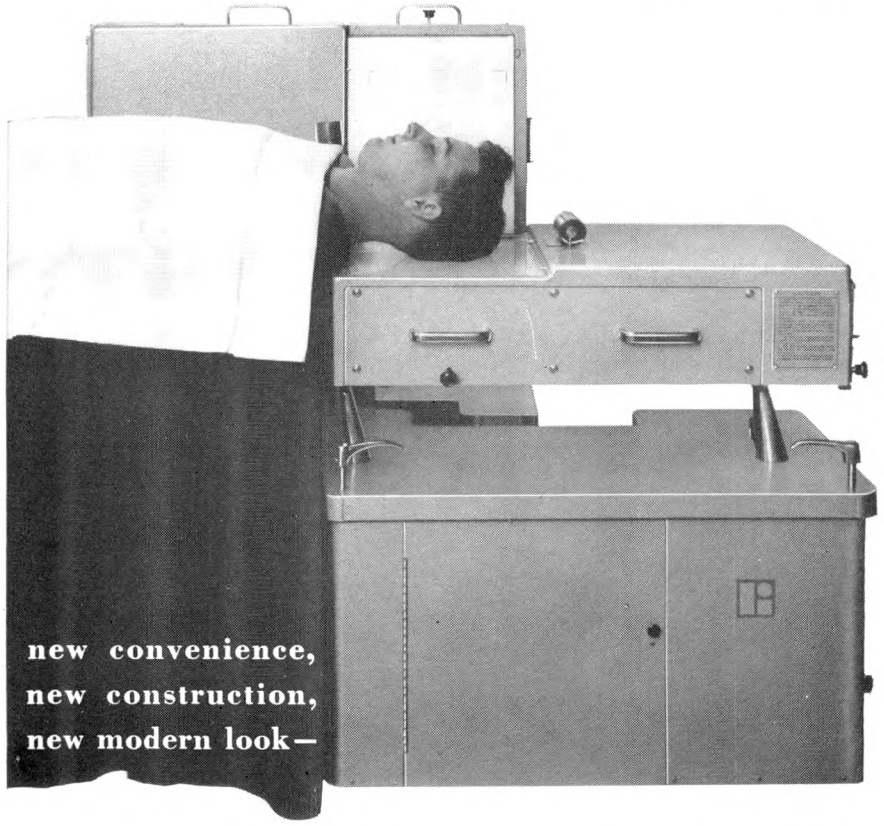
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For more detailed information, contact your General Electric representative, or write directly to X-Ray Department, General Electric Company, Milwaukee 1, Wisconsin. Ask for Publication A-21.

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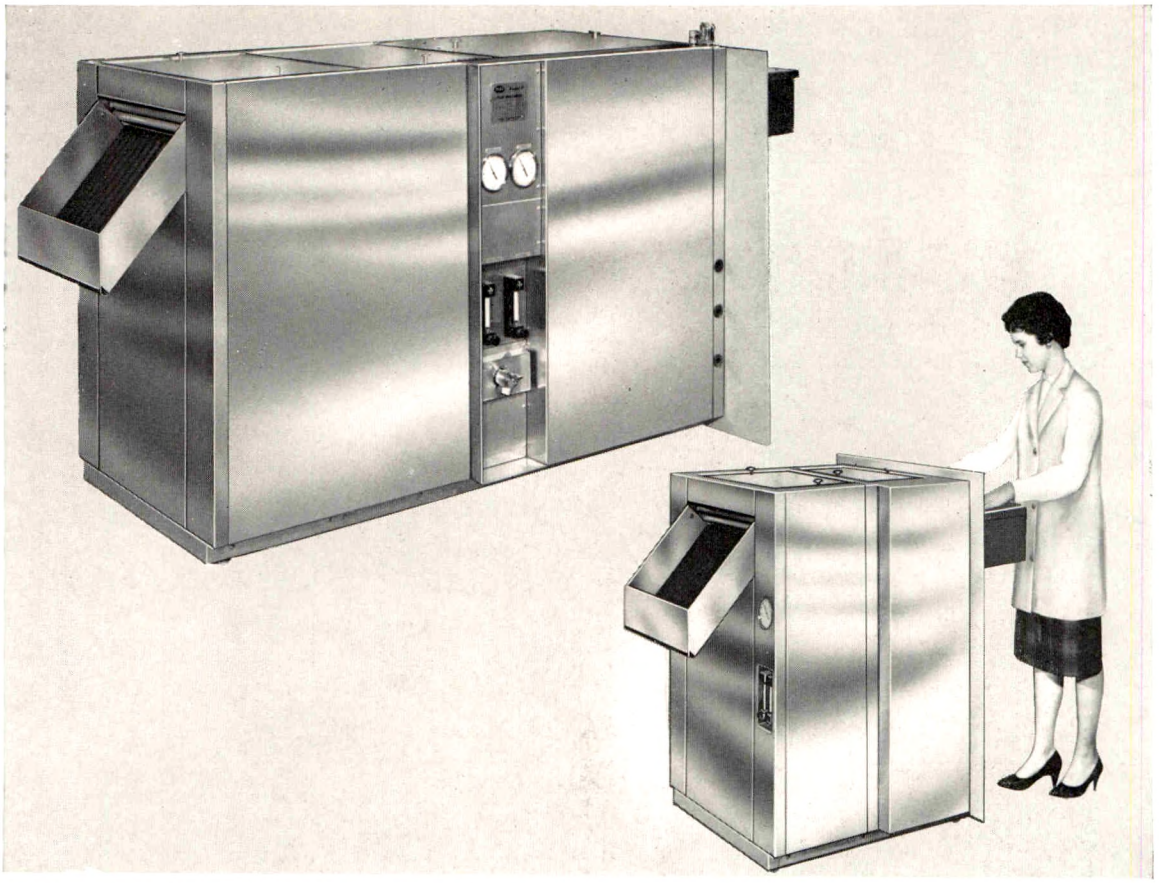
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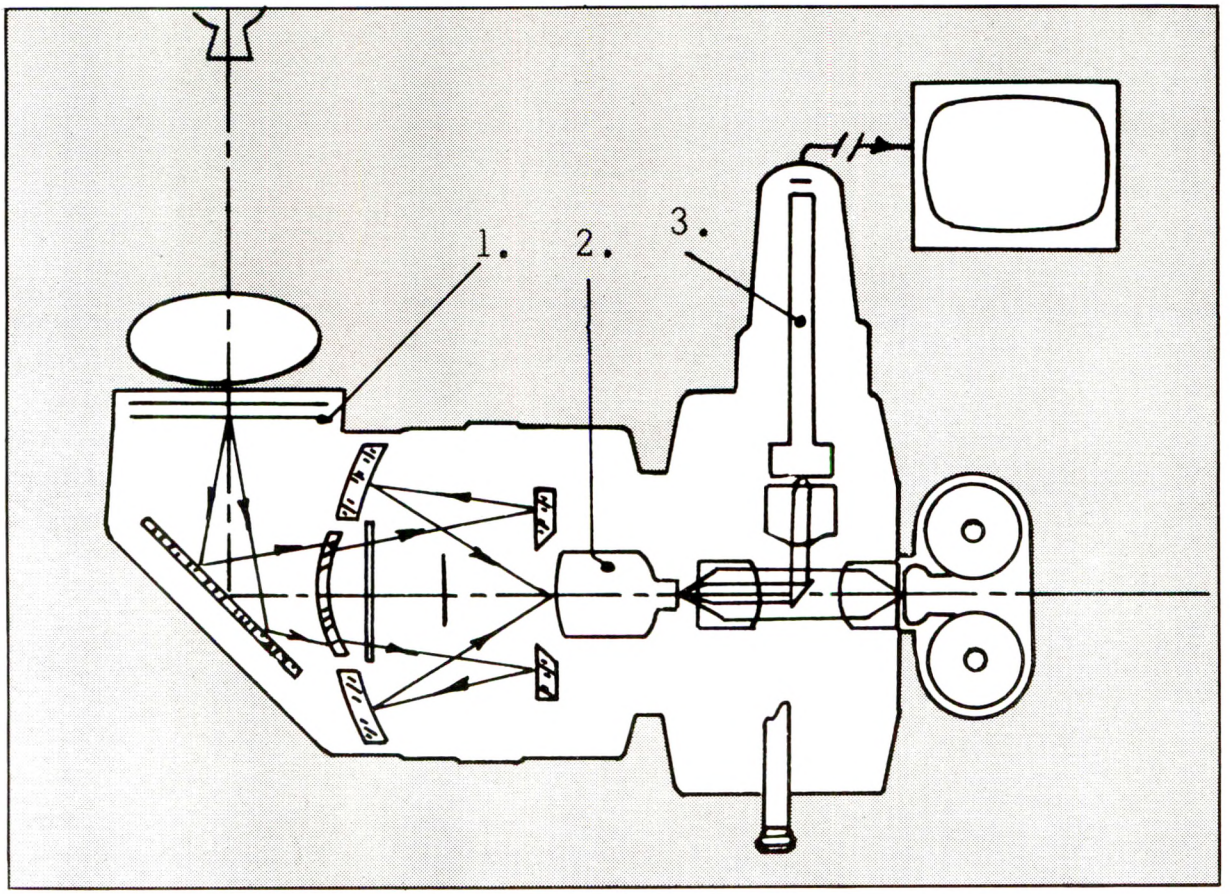
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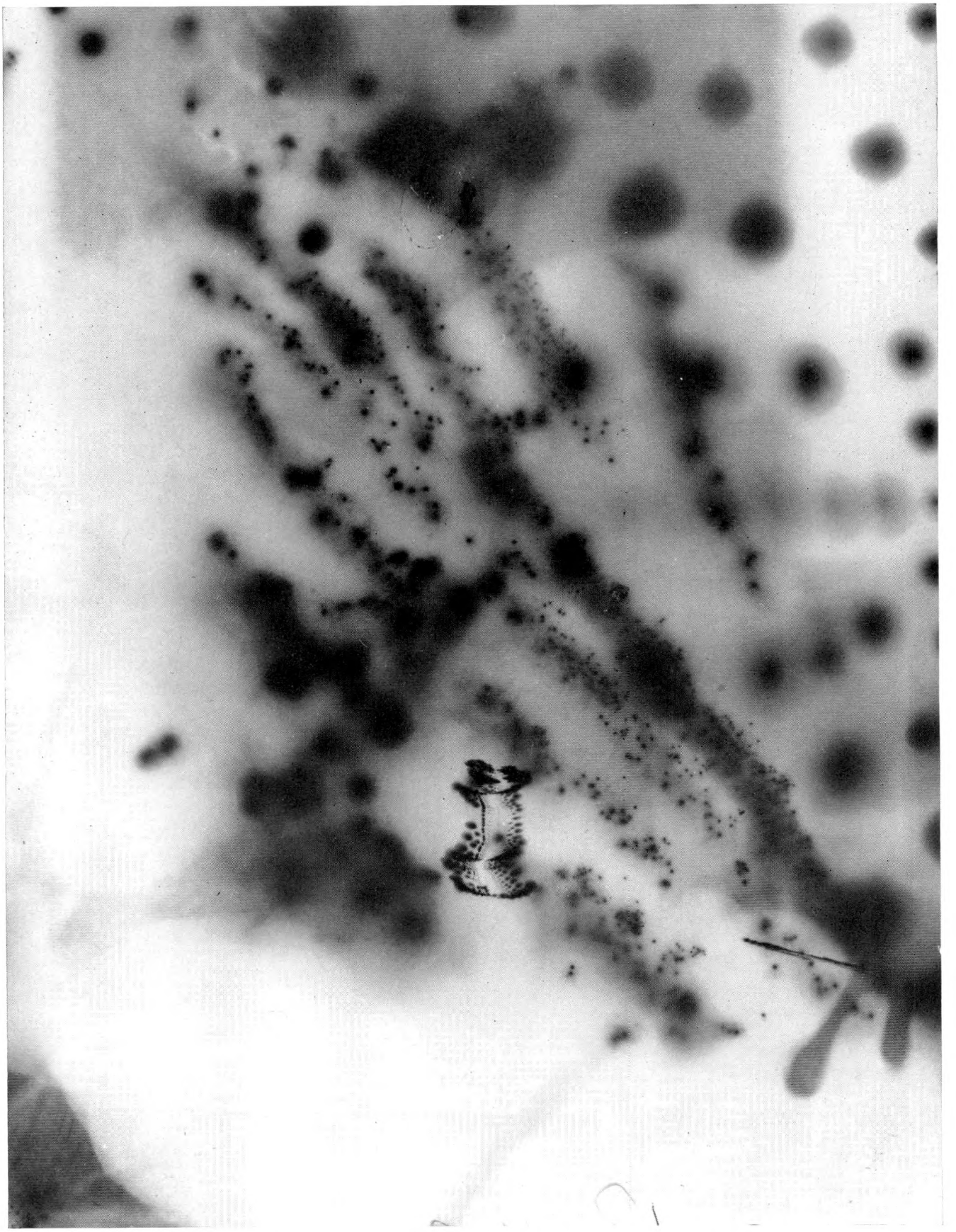
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A Symposium
Held Under the Auspices of the
Division of Radiological Health
United States Public Health Service
Washington, D.C., March 5-6, 1962

TECHNOLOGICAL NEEDS FOR REDUCTION OF PATIENT DOSAGE FROM DIAGNOSTIC RADIOLOGY

Edited by

MURRAY L. JANOWER
Department of Radiology
Massachusetts General Hospital
Boston, Massachusetts

This volume is the **first** to cover in *one source* the manifold aspects of the problem of reduction of patient dose from diagnostic radiology.

The discussion begins *logically* with a consideration of measurement techniques suitable for the low energy, low dose radiation encountered in diagnostic radiology. The properties of ionization chambers, scintillation counters, film and chemical, glass and thermoluminescent dosimeters are reviewed . . . their characteristics of size, sensitivity, precision, and energy dependence carefully determined.

The x-ray machine is then *scrutinized* for methods which might yield dose reductions. Kilovoltage, filtration, collimation, inspection practices, and dose monitoring equipment are thoroughly discussed.

Two sections of the book are devoted to image recording in radiography and fluoroscopy. Radiographic screens, films, and grids are discussed. Patient dosage from cinefluorography is explored. The *efficiency* of fluorescent screens and various properties of image intensifiers as related to patient dose are discussed.

January 1963 — *360 pages*
$6.75 — *154 illustrations*

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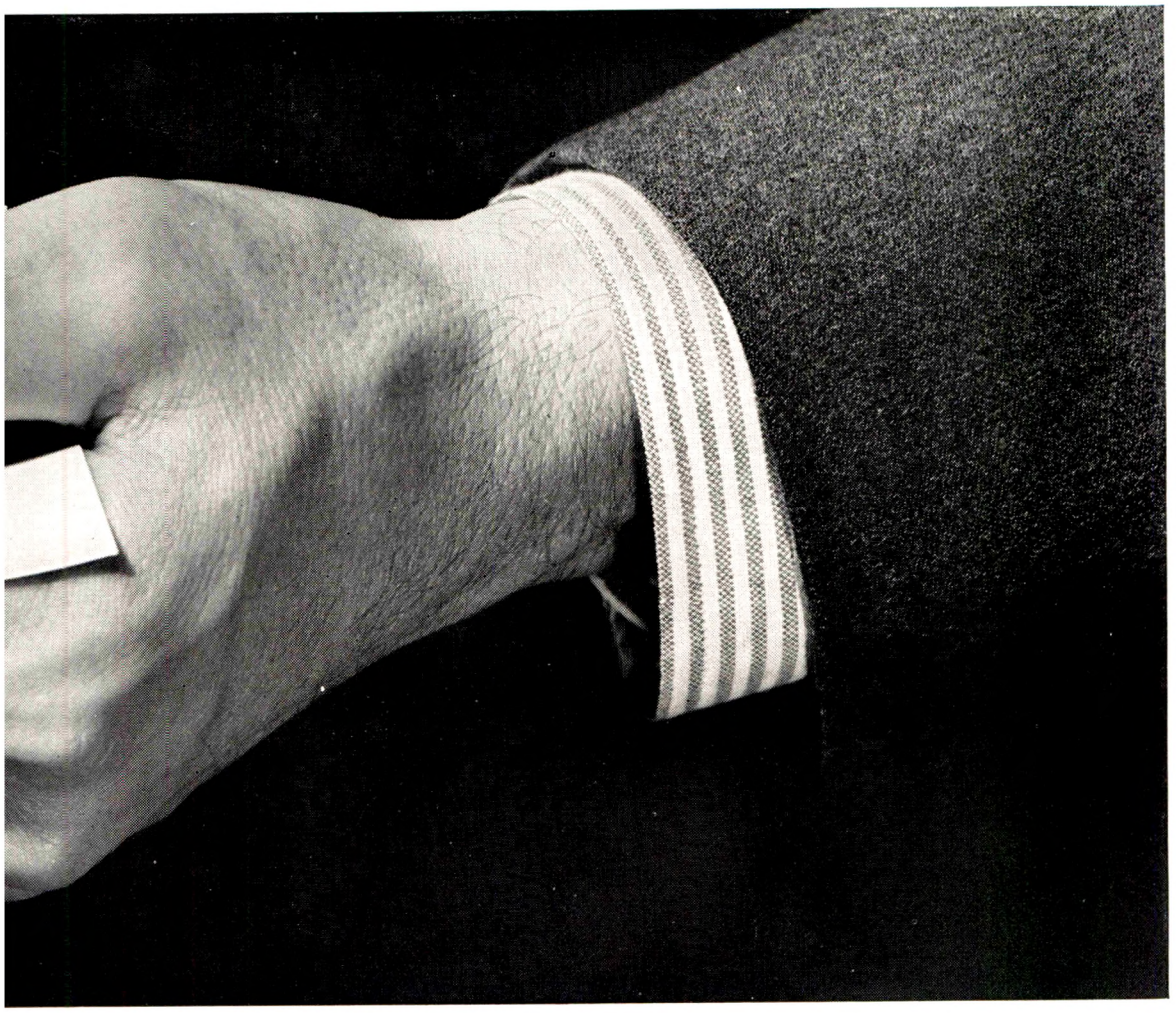
— Not just what it costs to buy . . . *but what it costs to keep x-ray equipment going over the years.* For a common thread running through everything General Electric produces is the determination not to leave customers out on a limb. Price-cutting has to take its "savings" from somewhere, and it's no secret that *help-after-installation* often becomes an irresistible place to chop.

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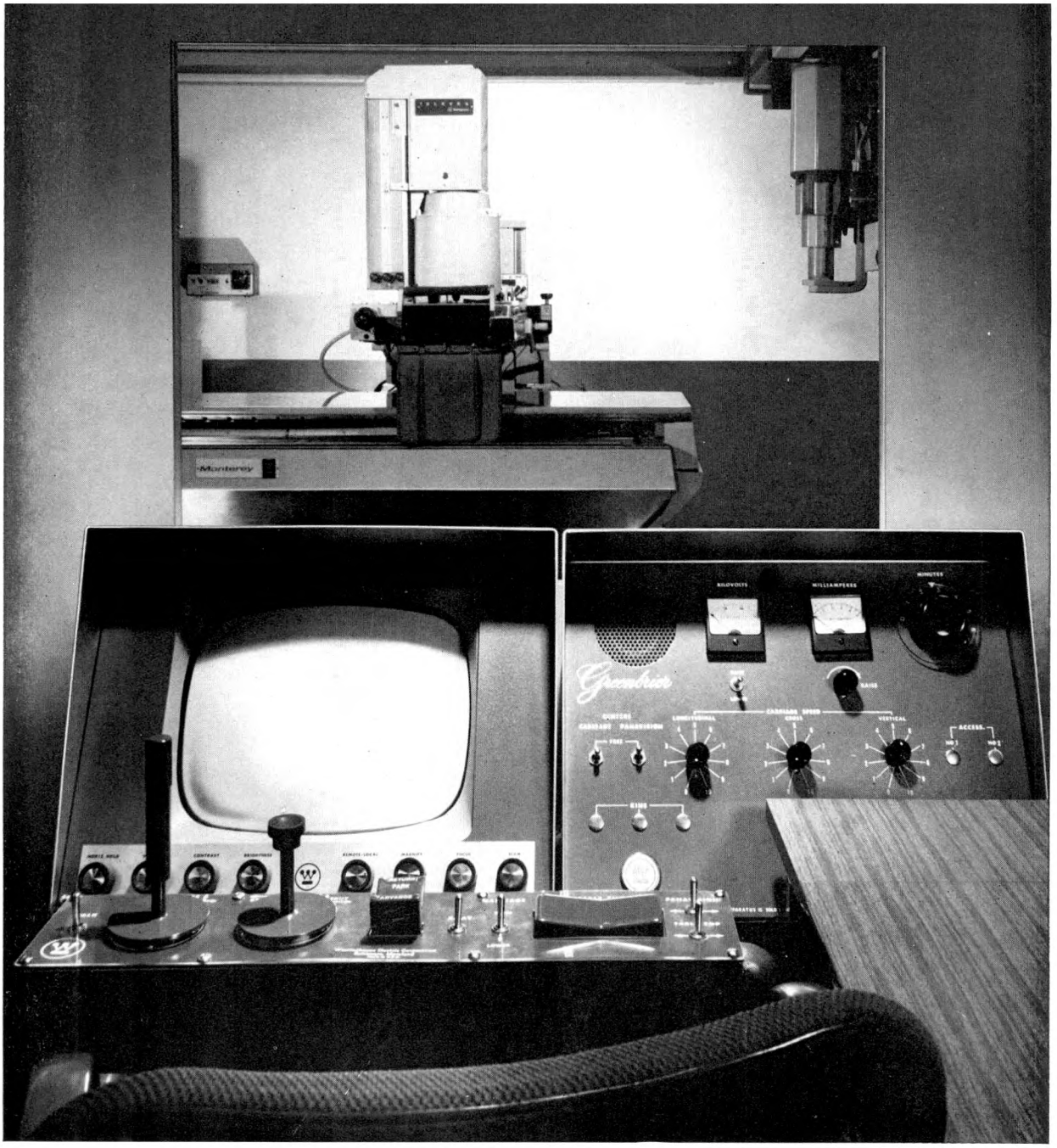
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THE AMERICAN JOURNAL OF ROENTGENOLOGY
RADIUM THERAPY AND NUCLEAR MEDICINE

VOL. 89 FEBRUARY, 1963 NO. 2

METHODS OF ALTERING CIRCULATORY DYNAMICS TO IMPROVE ROENTGEN EXAMINATION OF THE CARDIOVASCULAR SYSTEM*

CHAMBERLAIN LECTURE, 1961

By BJÖRN NORDENSTRÖM, M.D.
STOCKHOLM, SWEDEN

WHEN I first became interested in the fascinating field of diagnostic cardiovascular radiology, it was not long before I encountered in the literature a name that was later to recur time after time—W. Edward Chamberlain. His magnificent work, both from the qualitative and quantitative points of view, has resulted in advances of permanent value not only in diagnostic but also in therapeutic radiology. My first contact with his work was in the field of electrokymography. The brilliant idea which he worked out as long ago as 1945, for the first electrokymograph, meant a big step forward, particularly in the theoretic aspects of radiologic circulatory research. The dynamic changes in the motion of the heart and blood vessels can be studied with this instrument. It was probably not a matter of chance that this instrument was developed under Dr. Chamberlain's leadership at Temple University. His interest in hemodynamic problems, of course, began many years before this. As far back as 1927 he had worked out the so-called Ruggles-Chamberlain method for roentgenologic filming of the motion of the heart. For studies of the relation between the hemodynamics and the pressure conditions in the cerebrospinal fluid, he devised a craniovertebral cavity model, which is still in use for teaching purposes at the Temple University Medical School.

In addition to his interest in hemodynamic problems in the field of roentgen diagnosis, Dr. Chamberlain has, among other things, made valuable contributions in the field of stereoscopic roentgenology. He devised the first stereoscope as early as 1922, and during the 1930's he devised both biplane and multiplane fluoroscopes. Because of his experience and knowledge of the physical factors in medical fluoroscopy, he was already able, in the 1940's, to predict many of the rapid and valuable developments that have taken place in recent years in the electronic image-intensifier

* From the Department of Thoracic Radiology (Head, Björn Nordenström), Karolinska Sjukhuset, Stockholm, Sweden.
Presented at Temple University School of Medicine and Hospital, Philadelphia, Pennsylvania, November 22, 1961.

technique in fluoroscopy. In 1953, he devised and constructed a biplane stereoscopic angiocardiographic apparatus which since then has been in continuous use at the Temple University Hospital. I am not able to review in detail the entire range, both past and present, of Dr. Chamberlain's scientific activities, but even from what I have mentioned here it is obvious to all that we have before us one of the pioneers whose intense interest in science and techniques has meant so much to the rapid progress that is at present taking place in radiology.

ALTHOUGH we are beginning to be able to solve some physiologic problems and aspects by roentgenologic methods, morphology is nevertheless the foundation upon which radiologic diagnosis is most firmly based. In the examination of the stomach and intestines, for instance, a radiologist would under no circumstances think of examining the organs without exerting some influence on them from without. By compressing and squeezing the organ, we improve the possibilities of obtaining exact information on whether morphologic changes are present or not. Corresponding technical problems may arise in cardiovascular diagnostic examinations. The methods that can be used in conjunction with contrast examinations to study the morphology of the heart and blood vessels must be specially devised for the purpose. These methods are often closely related to physiologic procedures and may be divided into groups—mechanical and chemical methods.

MECHANICAL METHODS

One of the simplest ways of influencing the circulation mechanically is to utilize the effect of a rapid injection of the contrast medium. Normally, when contrast fluid is injected through catheters or cannulas into the cavities of the heart, it is not possible to alter the circulation to any appreciable extent.[34] When a defect in the ventricular septum is present and the differential pressure in the ventricles is diminished to a certain level, however, the defect may be visualized during a rapid injection of contrast medium. In such a case the injection may cause a temporary reversal of a shunt (Fig. 1).

In peripheral veins and arteries, the circulation can be readily influenced by a rapid injection. With a rapid injection in the femoral artery, for instance, the contrast medium can be forced in a retrograde direction up to a level beyond the bifurcation of the aorta. With a similar injection into the radial artery, contrast solution can be made to pass as far as the aorta.

External compression of blood vessels is a simple and useful method for influencing the circulation mechanically. When contrast medium is to be injected into the ascending aorta, it is sometimes desirable to reduce the flow of contrast material to the brain. This may be achieved by manual compression of the carotid artery.

In the case shown in Figure 2, a right

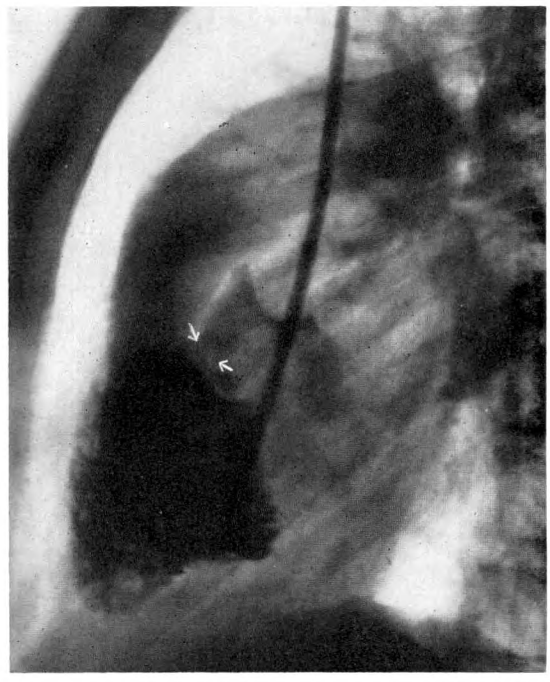


FIG. 1. Ventricular septal defect. Reversal of a left-to-right shunt into a right-to-left shunt by means of a rapid injection of contrast material into the right ventricle. Arrows indicate size and position of the defect.



Fig. 2. Conventional selective cardioangiogram with contrast injection in the right atrium. The contrast material flows only through the left pulmonary artery due to atresia of the right pulmonary artery.

pulmonary artery atresia was diagnosed by "conventional" cardioangiography. We wanted, however, also to obtain information about the morphology of the lung vessels distal to the atresia. A contrast medium was for that purpose slowly injected at the origin of the internal mammary artery through a catheter (Fig. 3*a*). Most of the contrast solution could be directed to the right internal mammary artery by manual compression of the neck vessels and the application of a rubber cuff which was well inflated around the right upper arm. The object was to perfuse the internal mammary artery, its mediastinal tributaries and via their communications with the bronchial arteries to reach the lung vessels, which anastomose with the bronchial vessels. In later stages of the contrast material perfusion, which could be accomplished by use of this simple external compression of vessels, filling was obtained of the lung vessels distal to the atretic segment of the right pulmonary artery (Fig. 3*b*).

When contrast medium is injected into the common iliac artery, an increased amount of it can be diverted into vessels of the pelvic organs by applying external compression of the femoral arteries as devised by Fernström.[24] This considerably improves the diagnostic possibilities. In the case shown in Figure 4 both femoral arteries were compressed during injection of the contrast material in the lower part of the abdominal aorta through a catheter introduced in the right femoral artery. Due to the compression the contrast material is directed to the internal iliac artery and its tributaries. The arteriovenous communications of an old interstitial tubal pregnancy on the right side could be demonstrated in this fashion.

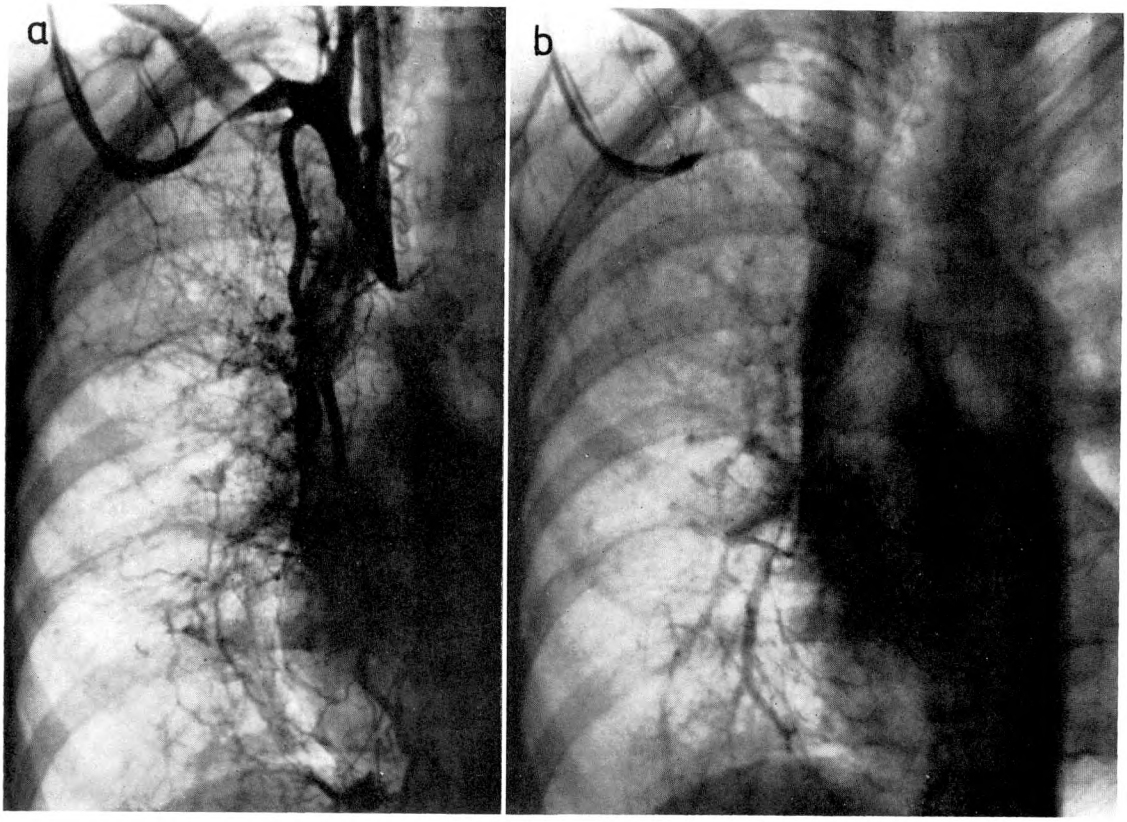
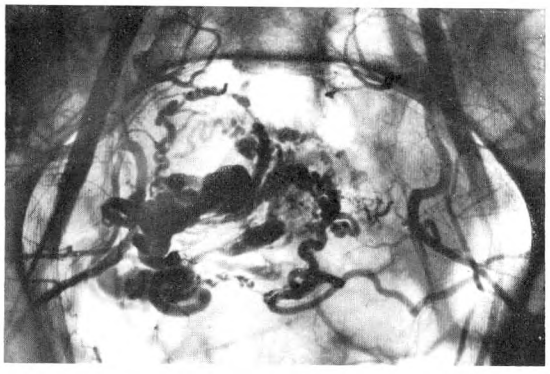


Fig. 3. Same case as in Figure 2. (*a*) By external compression of the carotid artery and the right brachial artery, contrast material is directed into the internal mammary artery. (*b*) Through the internal mammary artery, its tributaries in the mediastinum and their communication with the bronchial arteries, the pulmonary vessels distal to the atretic segment of the right lung are visualized via the bronchopulmonary vascular communications.

In examination of varicose veins of the lower limbs, it is important, prior to surgical intervention, to ascertain whether the deep veins are patent or not.[26,31] An elastic bandage is therefore applied around the leg to compress the superficial veins before the contrast medium is injected into a toe or malleolar vein. Thus the contrast medium is directed to the deep veins of the lower leg. If the deep veins of the leg are open, the contrast medium will flow through them. In the patient in Figure 5, the contrast material was directed into patent deep veins in this manner.



The circulation in the abdominal aorta and inferior vena cava can likewise be influenced by external compression. External compression of the inferior vena cava has been extensively used by Helander and

Fig. 4. Old interstitial tubal pregnancy on the right side with development of arteriovenous communications. Contrast material is directed into the internal iliac arteries by external compression of the femoral arteries on both sides. (Courtesy Dr. I. Fernström.)

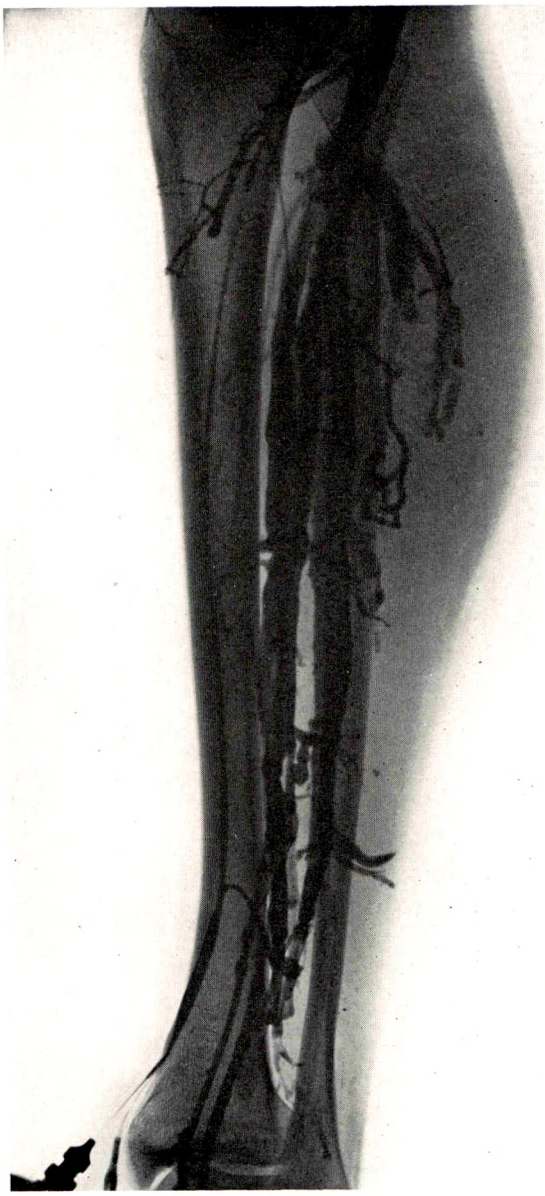


Fig. 5. Varicose superficial veins are compressed after wrapping the leg with a tourniquet. Contrast material is injected in a superficial malleolar vein. It is directed by the compression into the deep veins which are patent.

Lindbom[27] in their investigations of the relations of tumors and lymph nodes to the vena cava. In Figure 6 normal iliac veins and their tributaries are visualized after external compression of the inferior vena cava and simultaneous injection of contrast medium in the femoral veins.

As a rule, it is difficult, especially in obese patients, to achieve effective external compression of the large abdominal vessels. It is, of course, impossible within the chest. In such patients balloon catheters may be used. Figure 7, *a–g* shows some of our catheters constructed for various roentgen diagnostic purposes.[32] When a balloon catheter is inserted via a peripheral vein, it can be passed through the right atrium and right ventricle and into the pulmonary artery. It has also been demonstrated[4] that it is possible to occlude one of the two pulmonary arteries with a balloon catheter in the dog as well as in man without producing any serious reactions. No venous blood then flows through the pulmonary artery of that side, and the oxygen uptake from that lung is prevented while at the same time the uptake of the contralateral lung increases.

Contrast material may now be injected into the main trunk of the pulmonary artery while one of the pulmonary arteries

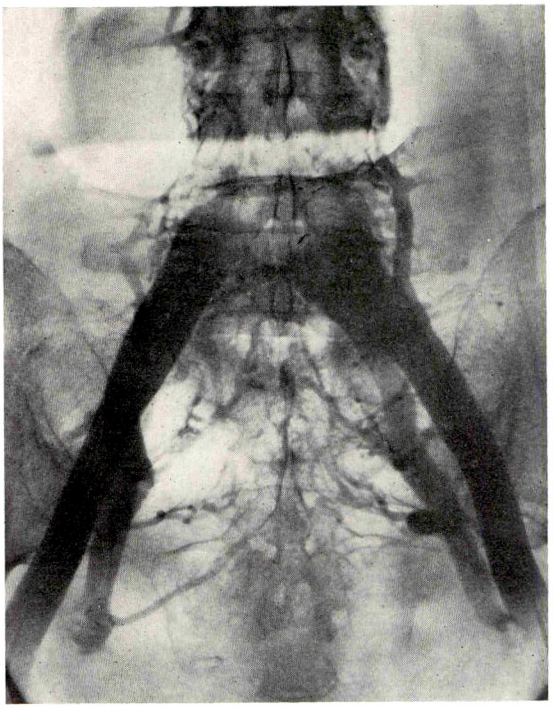


Fig. 6. Visualization of normal pelvic veins after injection of contrast material into both femoral veins and external compression of the lower part of the inferior vena cava. (Courtesy Dr. Å Lindbom.)

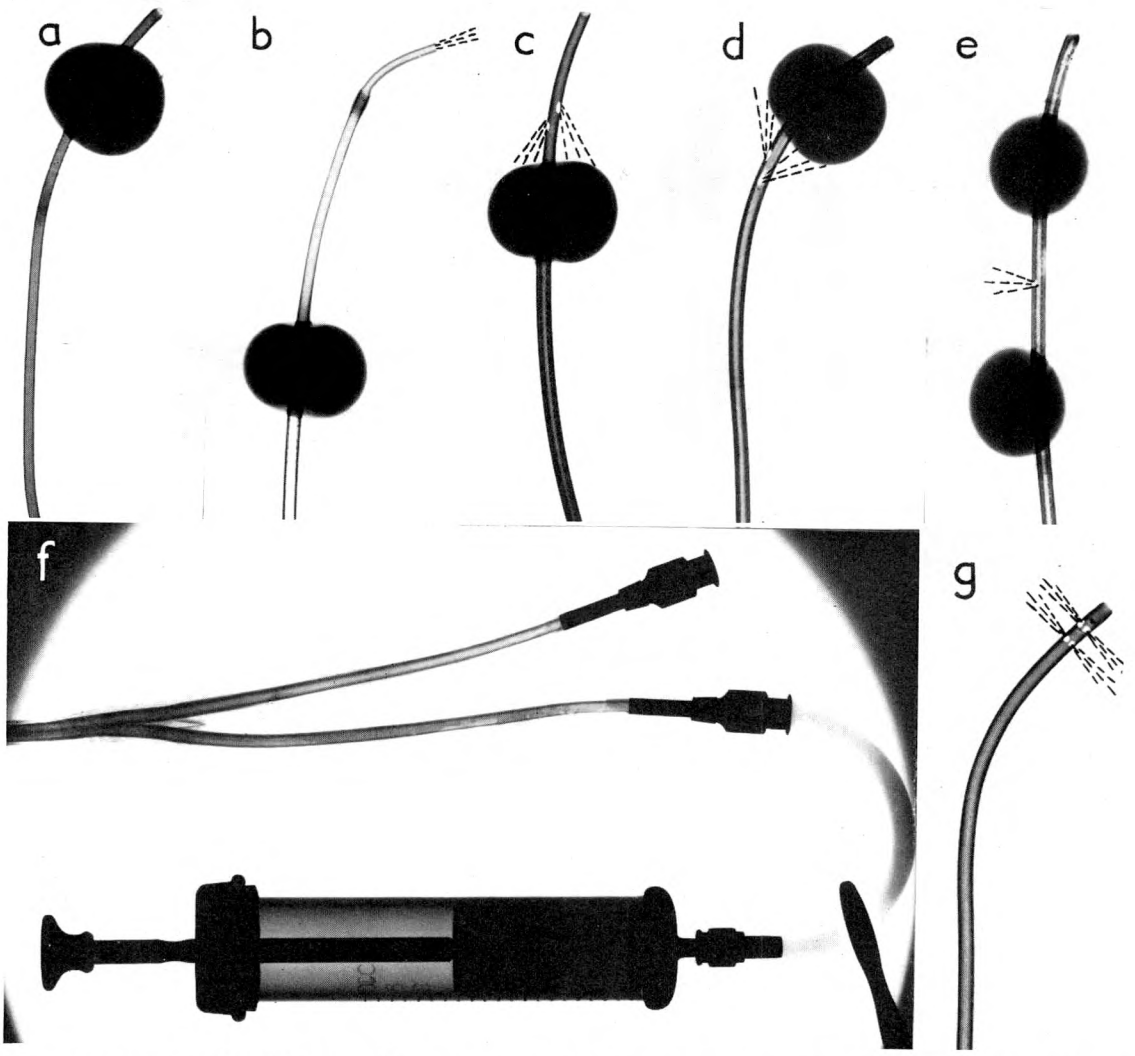


FIG. 7. Different kinds of balloon catheters constructed for roentgen diagnostic purposes (*a–f*). "Recoil free" single lumen catheter with blocked tip and side holes (*g*). On rapid injection the jets of liquid balance each other.

is occluded. The contrast medium will flow only through the contralateral lung (Fig. 8*a*), and we obtain by this means a unilateral pulmonary angiogram making a lateral view possible in which there is no superimposition of contrast-filled vessels of both lungs (Fig. 8*b*).

When contrast medium is injected distal to the occluding balloon through a separate channel in the catheter, it disappears from the artery very slowly. It is thus possible to carry out, without the aid of film changers or rapid cameras, a morphologic examination of the vessel of that lung. Figure 9, *a* and *b* shows a patient with an arteriovenous aneurysm of the left lung who was examined in this way.

Figure 10*a* shows a patient with a so-called middle lobe syndrome. Bronchiectasis is present in the middle lobe as may be seen on the bronchogram (Fig. 10*b*). In the corresponding angiogram (Fig. 10*a*) with contrast medium injection distal to the occlusion, one can see that the middle lobe artery is obliterated.

A balloon occlusion of the thoracic aorta

is also possible to perform.[32,36] When the thoracic aorta is occluded and the contrast medium is injected above the occlusion, good contrast filling of the intercostal, bronchial and mediastinal arteries may be obtained. In Figure 11 normal, narrow bronchial arteries of both lungs may be seen in a patient with a tuberculoma in the right lower lobe. Via the right bronchial artery, a small branch belonging to the pulmonary vessels was also contrast filled at the upper margin of the tumor.

When the abdominal aorta is occluded and contrast medium injected above the occlusion, the contrast medium can be directed to different abdominal arterial branches. Figure 12, *a* and *b* shows such an examination in a patient with injection of contrast medium of low concentration above the temporarily blocked abdominal aorta. The arterial phase is seen in Figure 12*a*, where the contrast material is filling the celiac artery and its branches. During subsequent phases a diffuse contrast material accumulation was observed in the pancreas (Fig. 12*b*). Later this contrast material accumulation slowly disappeared.

Contrast material filling of the renal vessels, the inferior phrenic arteries and others can also be obtained by using balloon catheters. One of the big problems in connection with these examinations, however, is the tolerance of the spinal cord to the contrast medium. The concentration, volume and the particular type of contrast material must be carefully chosen with a large margin of safety in mind.[36]

It shall also be mentioned that Dotter and Frische[23] have lately taken up a variation of this technique. By occluding the ascending aorta followed by an injection of contrast material above the aortic valve, they endeavor to direct the contrast medium to the coronary arteries and thereby achieve maximum contrast filling of these vessels.

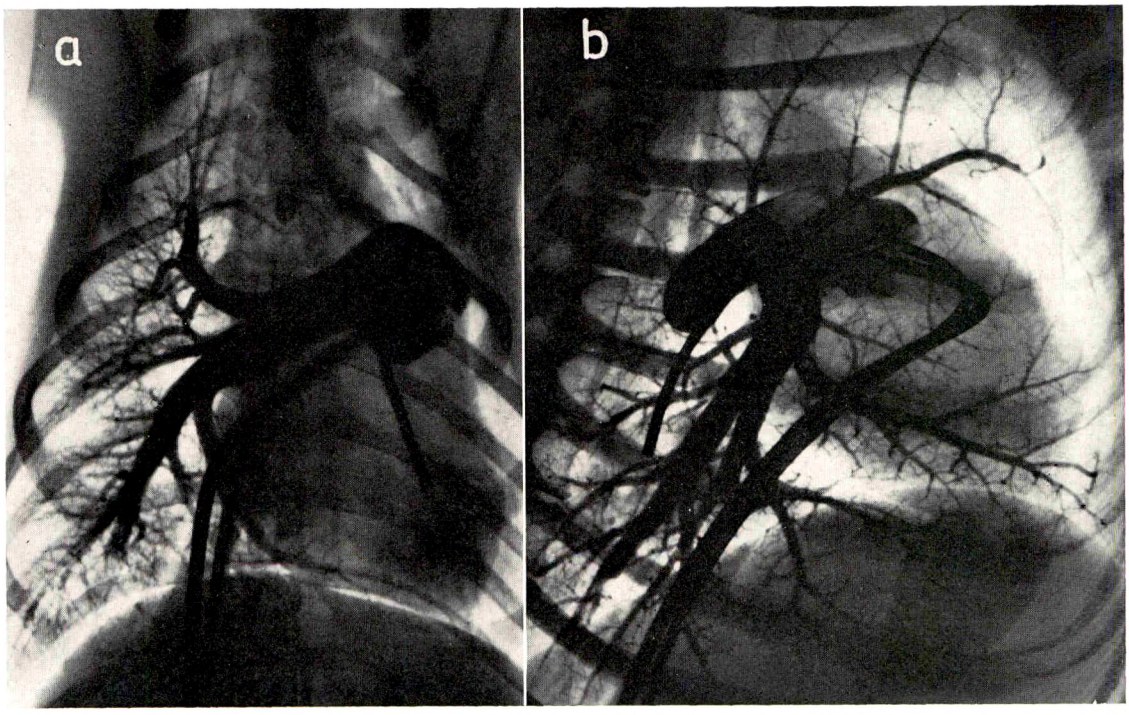


Fig. 8. (*a*) Unilateral angiogram of the pulmonary vessels of the right lung during temporary occlusion of the left pulmonary artery. The contrast material injected proximal to the occlusion flows only through the vessels of the right lung. (*b*) In the lateral view there is no superimposition of contrast vessels from the left lung.

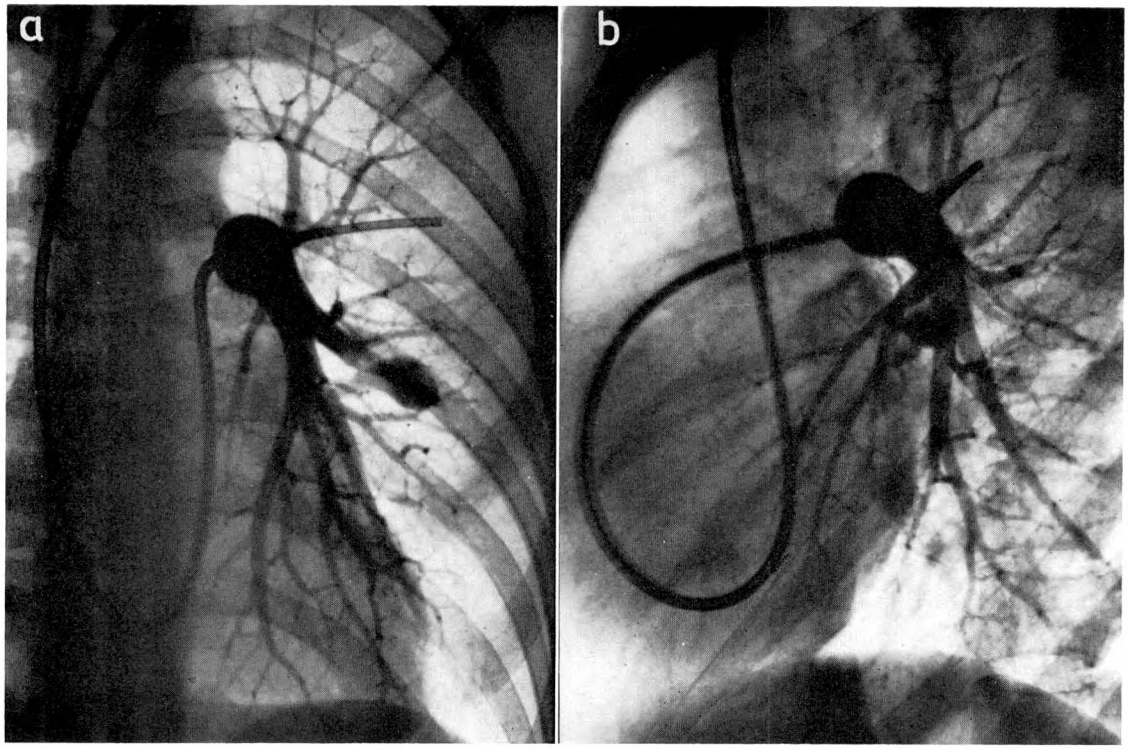
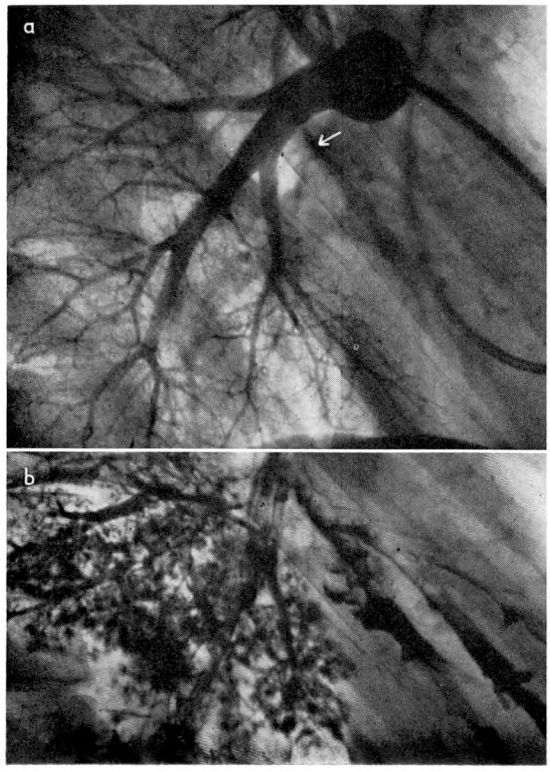


Fig. 9. (*a* and *b*) Solitary arteriovenous aneurysm of the lingula pulmonis visualized after injection of a small dose of contrast material distal to the occluding balloon.



Balloon catheters can also be used in the venous system. The azygos vein for instance can easily be catheterized from below and occluded by a balloon catheter. Its branches can be filled in retrograde fashion by contrast material injection distal to the occlusion. In Figure 13 the azygos and its mediastinal venous communications are visualized in a case of bronchial carcinoma with atelectasis of the left lung.

The azygos system and the internal venous plexus of the spine[33] can likewise be filled after temporary occlusion of the inferior vena cava and injection of contrast medium below the occlusion (Fig. 14, *a* and *b*).

In Figure 15, *a* and *b* a double balloon

Fig. 10. So-called middle lobe syndrome and pulmonary emphysema. (*a*) Selective arteriogram. (*b*) Bronchogram. The middle lobe artery is obliterated (arrow) and the middle lobe bronchus is ectatic.

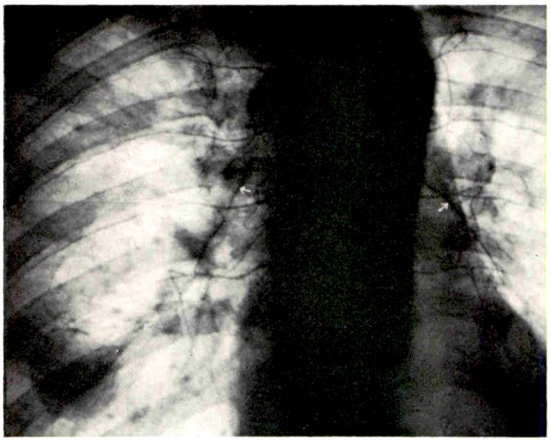


Fig. 11. Visualization of normal sized bronchial and intercostal arteries of the left and right lung after temporary occlusion of the descending thoracic aorta and contrast material injection above the occlusion. Tuberculoma is seen basally in the right lung.

occlusion of the inferior vena cava in a patient is shown. Contrast medium was injected through an extra canal between these two balloons. The small vessel of a previously attempted, though not very effective, shunt operation for portal hypertension was visualized in this way. It may be of interest in this connection to mention

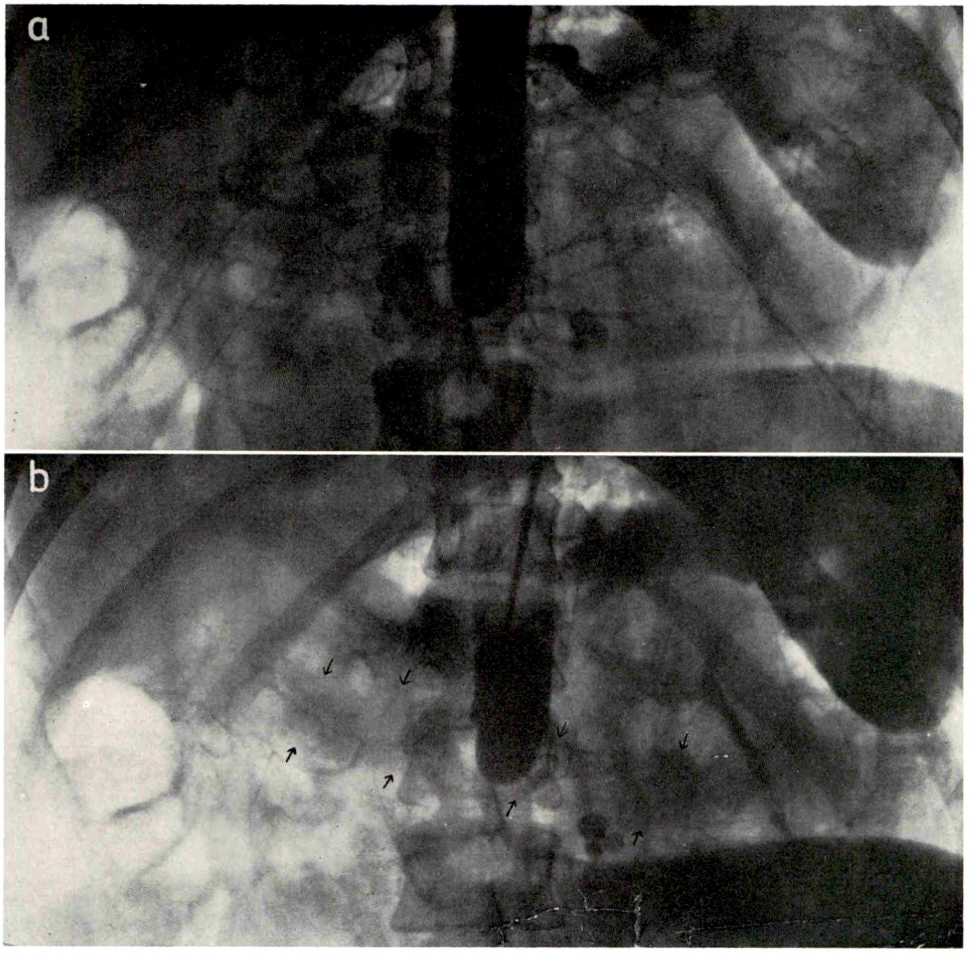


Fig. 12. Temporary occlusion of the abdominal aorta with contrast material injection above the occlusion. (*a*) Arterial phase shows contrast visualization of the tributaries of the celiac artery. (*b*) A slight accumulation of contrast material appears in the region of the pancreas. This contrast shadow slowly increased and then decreased in density during roentgenography.

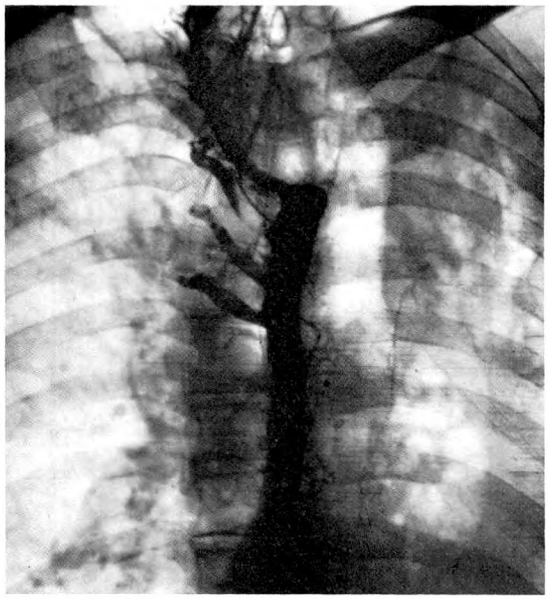


Fig. 13. Total atelectasis of the left lung due to a centrally growing carcinoma. The azygos vein is catheterized from below and temporarily occluded with a balloon. Contrast material is then injected distal to the occlusion. Retrograde contrast filling is obtained of the azygos vein and its tributaries in the mediastinum.

that animal experiments are going on to visualize the kidney veins by using the same technique (Fig. 16).

Occlusion of the inferior vena cava with a balloon results in a considerably diminished cardiac output.[33] If contrast medium is injected into the ascending aorta during occlusion of the inferior vena cava, improved visualization of, for instance, the coronary arteries is obtained.

Balloon catheters have also proved useful in the diagnosis of cardiac malformations. By temporarily occluding an atrial septal defect with a balloon[38] and then injecting contrast medium in the main trunk of the pulmonary artery,[28] it is possible to study whether other abnormal shunt communications are present as, for example, in abnormal pulmonary venous return. Many other possibilities exist. The technique has not by any means reached the limit of its usefulness.

Another method of mechanically influencing the circulation in connection with contrast studies is to increase the intrabronchial pressure. Celis and his co-workers[5] have used the Valsalva maneuver in connection with contrast studies. They found that the pulmonary vessels were better visualized with this procedure than without. Boerema and Blickman[3] got similar results by inflation of the lungs in dogs. The hemodynamic alterations produced when the lungs are inflated under narcosis are fairly well known by physiologists. Due to differences in physical properties between contrast medium and blood, a considerable deviation in dynamic behavior of the contrast medium and blood occurs when the basic hemodynamics are altered. Significant mistakes can therefore be made in the interpretation of the anatomy when an increase of the intrabronchial pressure is used. The circulatory changes produced can, however, also be utilized in many ways for diagnosis.[35]

The films shown in Figure 17, *a–d* are selective unilateral angiograms made by the use of an increase of the intrabronchial pressure. In this patient who suffered from pulmonary emphysema, a lower lobe lobectomy on the right side had been carried out earlier. A catheter was inserted through a peripheral vein and passed to the main trunk of the pulmonary artery. The patient was first placed on her right side. Under narcosis, the intrabronchial pressure was raised in the lungs for a short period, by insufflation of oxygen, to 35 cm. of water. As the contrast medium is heavier than the blood and as the circulation had been sufficiently slowed down by the rise of intrabronchial pressure, layering of the contrast medium took place and moved only to the right lung. With this technique, a unilateral angiogram of the pulmonary vessels of the dependent lung was obtained which made it possible to assess these vessels on the right side in a true lateral projection as well, without any contrast filling of the vessels from the contralateral lung (Fig. 17, *a* and *b*). With the catheter in the same position, the patient was then placed on her left side. After renewed inflation of the lungs to

a pressure of 35 cm. of water, another small dose of contrast medium was injected through the catheter. Layering of the contrast medium in the left lung then took place and a selective angiogram of the vessels of the left lung was obtained (Fig. 17, *c* and *d*).

Using a similar technique with controlled elevation of the intrabronchial pressure, it is possible to visualize, for instance, the coronary arteries by layering of the contrast material (Fig. 18).

If one desires to carry out selective angiography of the celiac artery and its tributaries by layering of the contrast material during retarded circulation (Fig. 19, *a* and *b*), the patient should be placed in the prone position. The pressure in the bronchi is then increased to a level that will decelerate the circulation sufficiently to allow con-

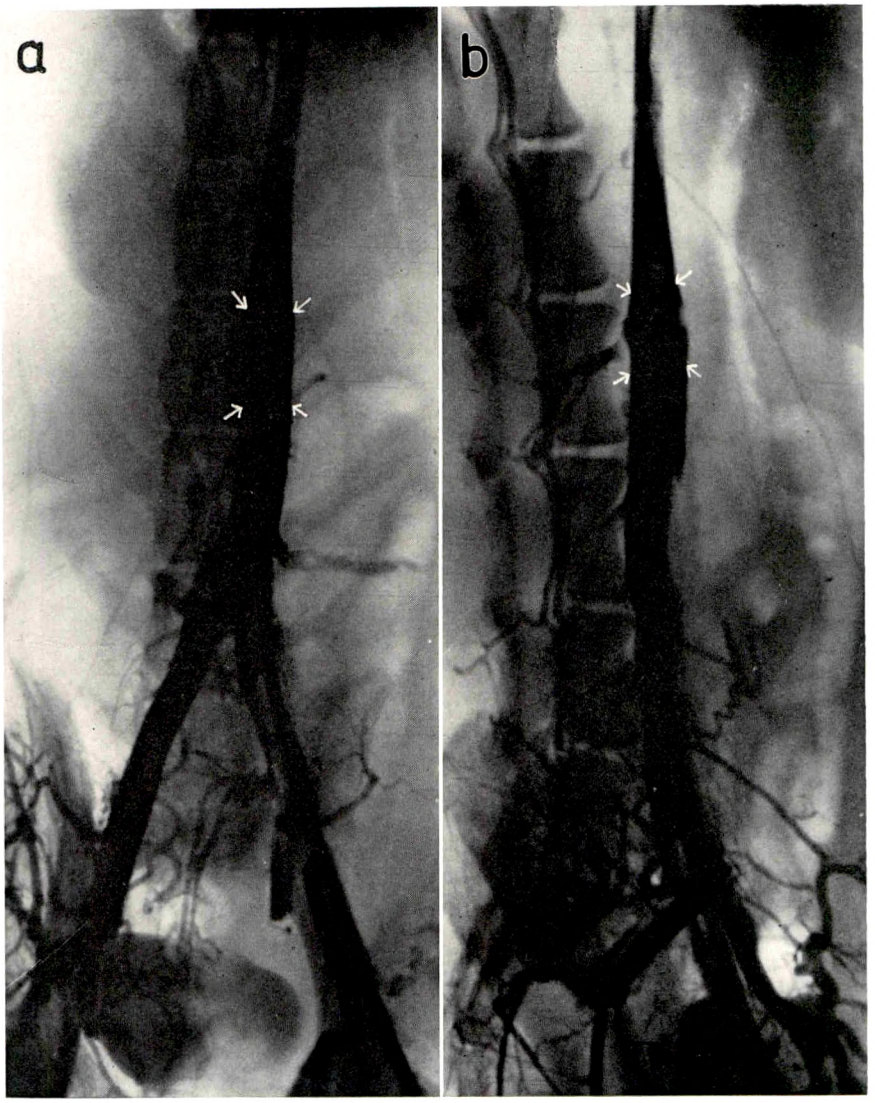


Fig. 14. Contrast visualization of the internal venous plexus of the spine in a dog. (*a*) Frontal and (*b*) lateral projections. The inferior vena cava is temporarily occluded by a balloon (arrows). Contrast material is injected below the occlusion and diverted over anastomotic lumbar vessels to the anterior internal venous plexus of the spine.

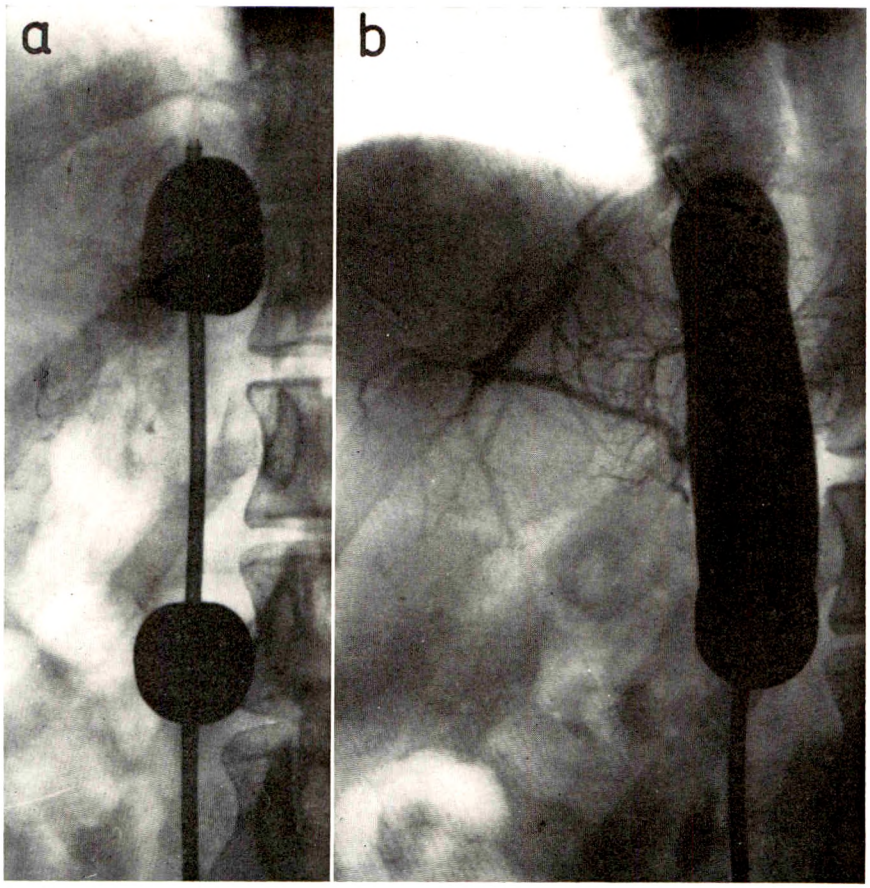


Fig. 15. (*a* and *b*) Temporary double occlusion of the inferior vena cava in a patient who previously had been operated on for portal hypertension. (*b*) The not very effective anastomosing vessel is visualized by contrast material injection between the occluding balloons.

trast layering. The contrast medium runs slowly down in the aorta during layering and into the celiac artery. A selective angiogram of the vessels of the celiac region is then obtained (Fig. 19*a*). In this case, the patient had severe cirrhosis of the liver. In a portogram (Fig. 19*b*) made later, pathologic vessels were visible in the portal vein and, in addition, a few varicosities were seen in close relation to the stomach.

Selective angiography of one of the kidneys is sometimes required, and can also be performed without selective catheterization by utilizing the layering principle (Fig. 20, *a* and *b*). The patient is placed in a decubitus position with the diseased kidney most dependent. When the blood flow is sufficiently decreased by inflation of the lungs, the contrast medium is injected in the first part of the thoracic aorta. It layers then and flows down into the dependent renal artery. Figure 20*a* shows the arterial phase, and Figure 20*b* the corresponding venous phase. Thus, it is not necessary to produce contrast filling of the kidney on the opposite side if visualization of the kidney on that side is not required.

The venous system can likewise be examined to a large extent by utilizing an increase of the intrabronchial pressure. The patient shown in Figure 21, *a* and *b* had an atrial septal defect with shunting of the blood from the left to the right atrium. Such defects can often be visualized by passing a catheter through the defect and

injecting the contrast medium into the left atrium. The contrast medium then flows through the defect which may be outlined. The passage of the contrast medium, however, takes place with great rapidity and it is often difficult to obtain detailed studies of the defect even when rapid film cameras are used. If the intrabronchial pressure is increased to a suitable level, the course of events can be considerably slowed down. The left-to-right shunt can even be reversed to a right-to-left shunt. When contrast medium is injected into the right atrium under these circumstances, it flows through the defect to the left atrium which allows a visualization of the communication between the atria (Fig. 21, *a* and *b*).

This technique may also be used in the manner shown in the the case in Figure 22, *a*, *b* and *c*. Here, there were abnormal pulmonary veins from the right upper and middle lobes emptying into the superior vena cava on the right side. In order to map out the anatomy, a catheter was introduced, and placed with its tip in the lower portion of the superior vena cava. In order to decrease the venous return to the heart, the intrabronchial pressure was raised by insufflation of oxygen. This means that a large amount of venous blood has accumulated in the abdominal vessels. Following a rapid injection of contrast medium through the catheter, the pressure in the bronchi was then decreased. The venous blood that had pooled chiefly in the abdominal vessels rapidly moved toward the heart. The blood rushing into the thoracic veins, together with the rapid injection of the contrast medium, contributed towards an elevation of the pressure in the right atrium and intrathoracic vena cava. In all probability, there was also a factor of suction in the abnormal veins during a short period of time when the intrabronchial pressure was released. All these factors cooperated in producing reversal of the flow and contrast filling of the abnormally terminating veins which can be seen in Figure 22, *a* and *b*. Their exact position and dimensions could thus be established. In this case, all the veins of the upper and middle lobes on the right side terminated in the right-sided superior vena cava. In addition, there was a small so-called sinus venous defect between the right and left atrium. This defect was also visualized on the roentgenograms by the produced reversal of flow between the atria (Fig. 22*c*). Besides these abnormalities, we found that this patient also had a left-sided superior vena cava. Another examination was therefore carried out with a balloon catheter, which was inserted through an arm vein on the left side (Fig. 23). It passed down into the left-sided superior vena cava which opened into a large coronary sinus terminating in the right atrium. By occluding portions of the left-sided superior vena cava step-by-step with the balloon, it was demonstrated that the patient could perfectly well tolerate an occlusion up to the level at which we see the balloon in Figure 23. When the balloon was placed at a higher level, disturbing signs of

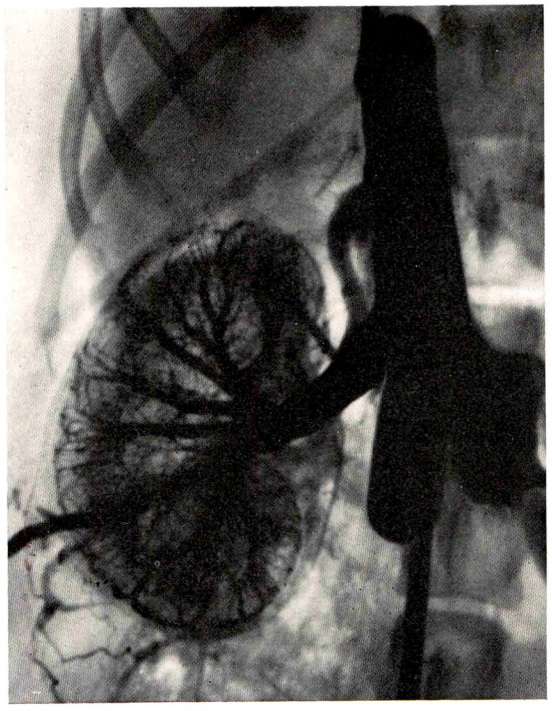


Fig. 16. Experimental retrograde venogram of the kidney in a dog. Contrast material is injected in the inferior vena cava between two occluding balloons.

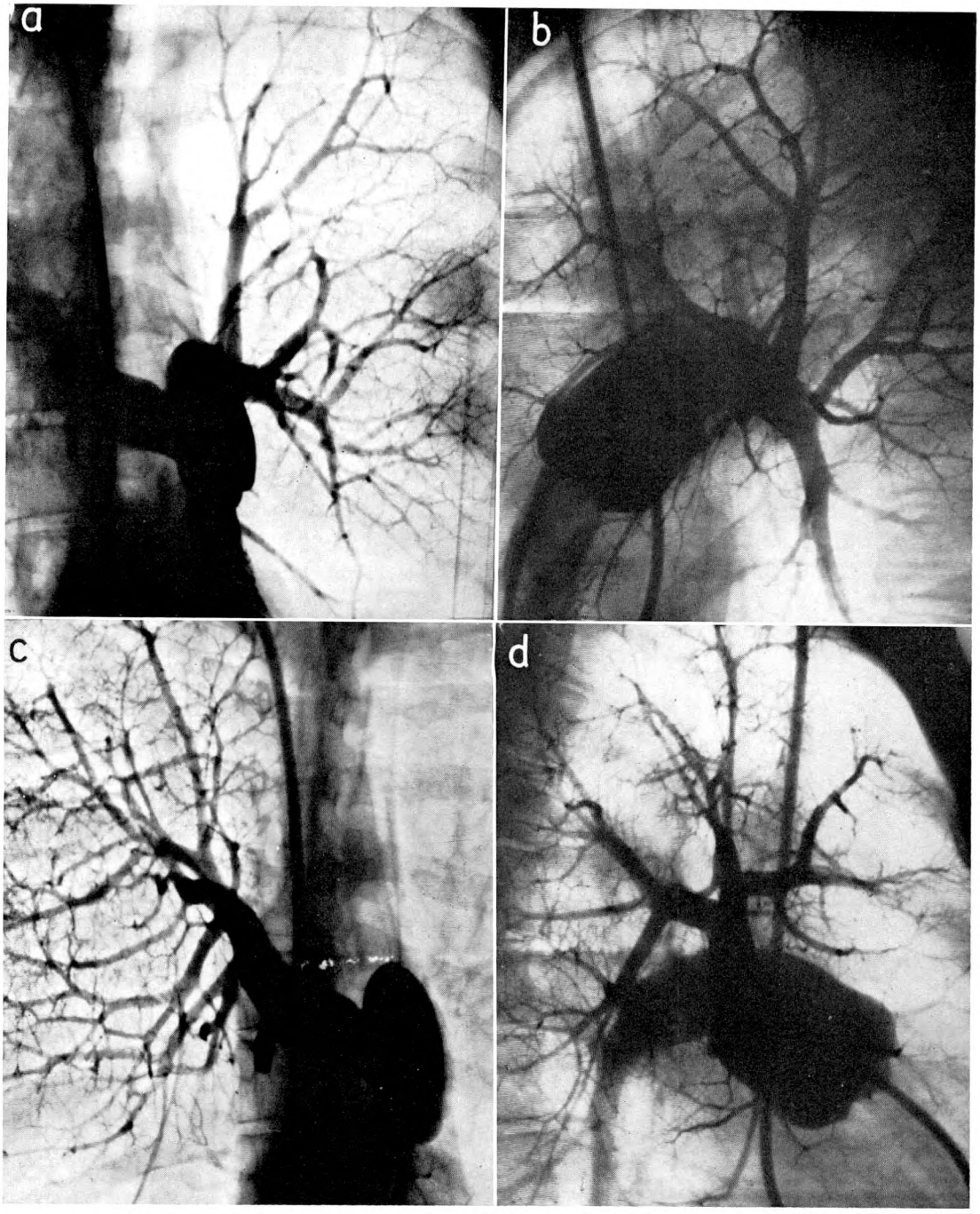


FIG. 17. Unilateral angiograms of the pulmonary vessels by means of layering of the contrast material during decreased blood flow produced by elevation of the intrabronchial pressure. (*a*) Anteroposterior and (*b*) lateral views with the patient lying on her left side. (*c*) Anteroposterior and (*d*) lateral views with the patient lying on her right side. The injections were both made in the main trunk of the pulmonary artery.

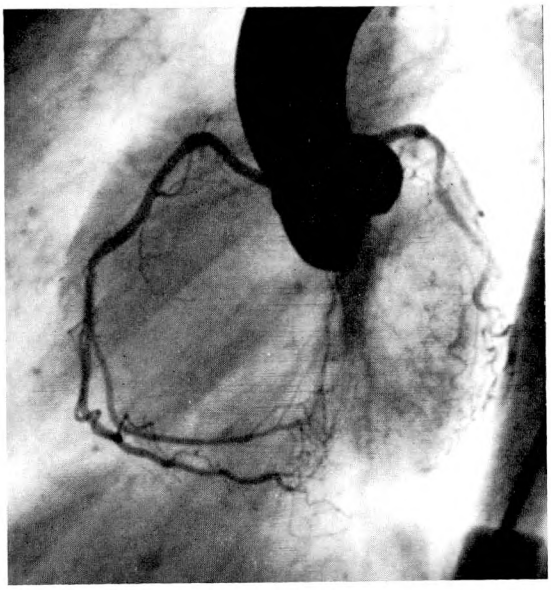


Fig. 18. Coronary angiogram with produced layering of the contrast material by reduction of output from the left ventricle through elevation of the intrabronchial pressure.

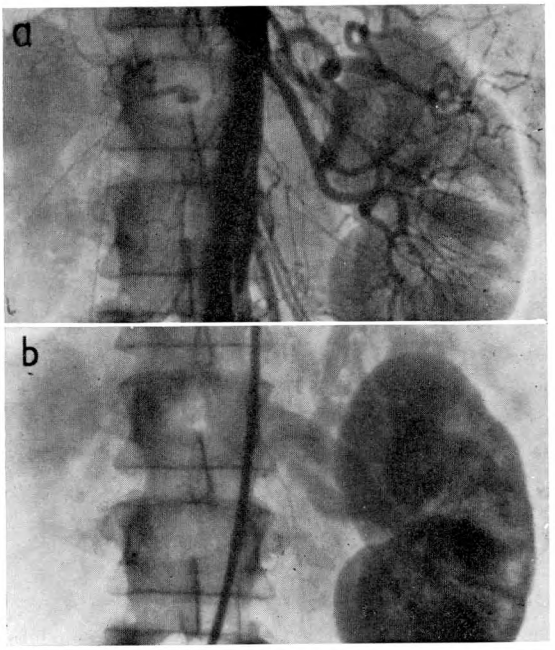
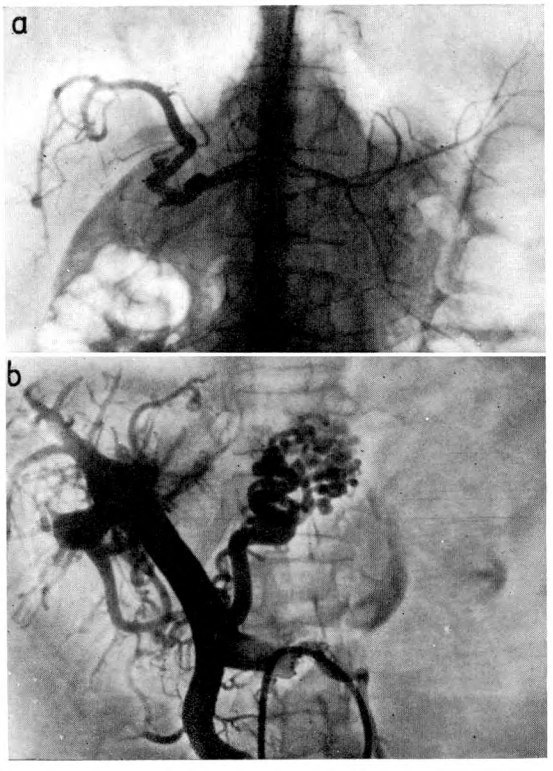


Fig. 20. Selective angiograms of the right kidney by layering of the contrast material. The patient was examined lying on his left side. Layering of the contrast medium was obtained by elevation of the intrabronchial pressure. Only the vessels of the left kidney are contrast filled. (*a*) Arterial phase. (*b*) Venous phase.



venous stasis in the head and left arm appeared. The pathways through which blood reached the right atrium from the head and left arm could then be established by injecting contrast medium above the occlusion. In Figure 23 one can see how the contrast medium passed through the hemiazygos and azygos vein to the right-sided superior vena cava. Some contrast material leaked between the balloon and the wall of the left-sided vena cava so that its lower portion and the enlarged coronary sinus were visualized.

Fig. 19. (*a*) Selective angiogram of the celiac artery with cirrhosis of the liver by layering of the contrast medium during elevation of the intrabronchial pressure with the patient in prone position. The hepatic artery is tortuous and the branches are compressed within the small liver. (*b*) The portal vessels are demonstrated for comparison. Some varices are present in the vicinity of the lower part of the esophagus.

The drawings in Figure 24 show the anatomy (*a*) before and (*b*) after the surgical correction which was carried out after these examinations. The operation was performed by suturing the lower part of the right-sided superior vena cava to the atrial septal defect and ligating the upper part of the right superior vena cava below the entrance of the azygos vein. The patient subsequently had no further discomfort, and the circulation was completely normal.

CHEMICAL METHODS

Narcosis has been used in connection with angiocardiography since the early 1940's. This was necessary partly because of the toxic side effects of the contrast media. Narcosis can also be utilized, however, to achieve a reliable apnea in the inspiratory state by moderate inflation of the lungs. This makes it possible to avoid respiratory motion blur on roentgenograms.

The next step was the introduction of succinylcholine iodide. The muscle relaxing effect of this substance produced complete relaxation of the skeletal and respiratory muscles under narcosis, and often, in addition, a reduction in the cardiac rate that contributed towards lessening the risk of motion unsharpness.

Several vasodilator agents have been employed. These have been tried mainly in connection with contrast studies of peripheral arteries and coronary arteries.[22] Oxyphylline, nitroglycerine, amyl nitrite, etc., have all been used.

It might be mentioned in this connection that in contrast media of the sodium acetrizoate group we recently found one of the most effective agents for dilata-

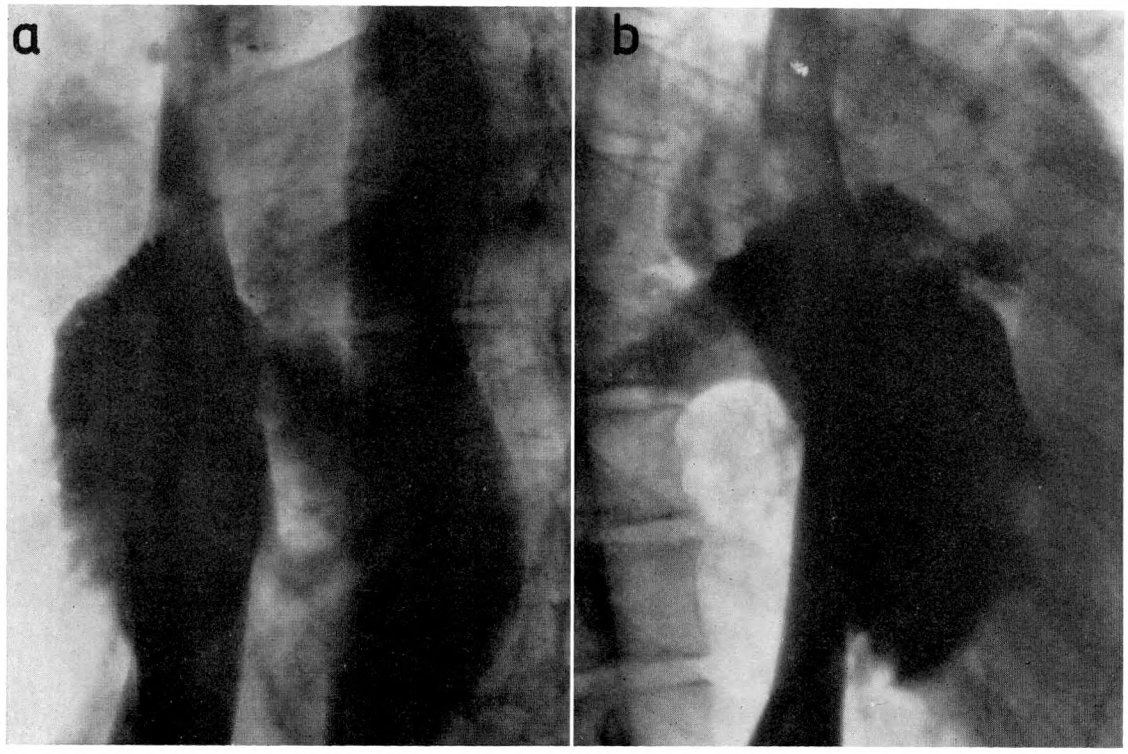


FIG. 21. (*a*) Reversal of flow in atrial septal defect and abnormally draining pulmonary veins. Left anterior oblique projection. The contrast medium filled the right atrium and the superior and inferior vena cava which are seen in the left part of the figure. From the right atrium the contrast material flowed through an atrial septal defect into the left atrium. (*b*) Right anterior oblique projection. Retrograde contrast filling is obtained in some large pulmonary veins emptying into the upper part of the right atrium and lower part of the superior vena cava.

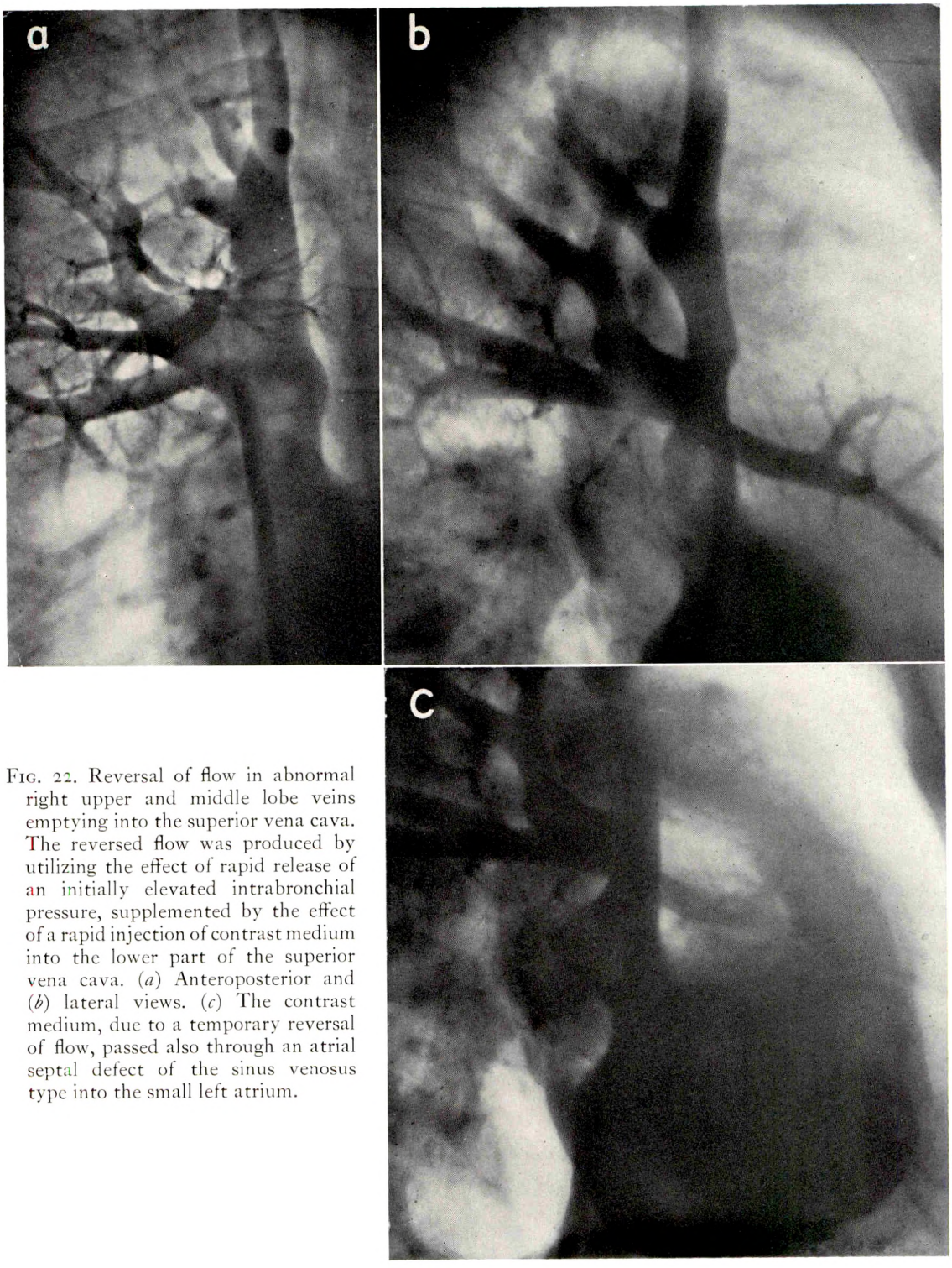


Fig. 22. Reversal of flow in abnormal right upper and middle lobe veins emptying into the superior vena cava. The reversed flow was produced by utilizing the effect of rapid release of an initially elevated intrabronchial pressure, supplemented by the effect of a rapid injection of contrast medium into the lower part of the superior vena cava. (*a*) Anteroposterior and (*b*) lateral views. (*c*) The contrast medium, due to a temporary reversal of flow, passed also through an atrial septal defect of the sinus venosus type into the small left atrium.

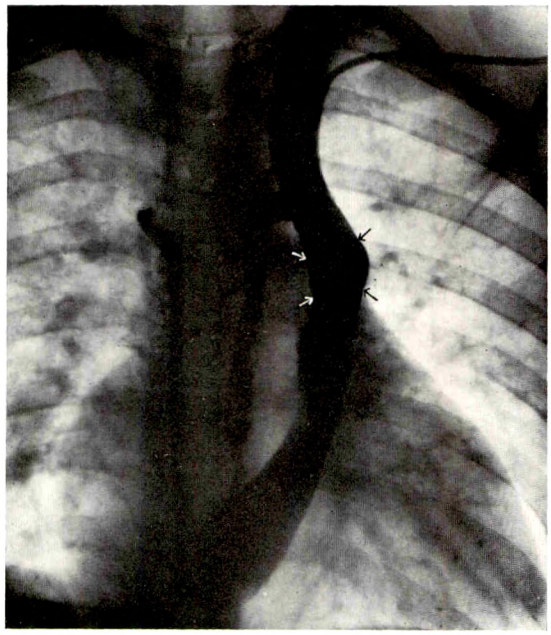


FIG. 23. Same case as shown in Figure 22. A left-sided superior vena cava was catheterized with a balloon catheter. Occlusion of the vena cava could be very well tolerated by the patient up to the level of the departure of the left-sided hemiazygos vein. Occlusion above this vein provoked severe stasis in the head and the left arm. Upon balloon occlusion (arrows) contrast material was injected above the balloon. Some of the contrast material passed between the balloon and the vessel wall to the lower part of the left-sided vena cava which empties via an enlarged coronary sinus into the right atrium. Other contrast material passed through the hemiazygos to the azygos vein, emptying into the right-sided superior vena cava.

tion of the peripheral vessels.[30] An example of the resultant roentgenograms is given in Figure 25, *a–d*. Half a milliliter per kilogram of body weight of thorotrast was injected in the femoral artery of a dog (Fig. 25*a*). The same volume of a sodium acetrizoate (rheopak) solution was then injected in a second series (Fig. 25*b*). In a third series (Fig. 25*c*) the same volume and concentration of the sodium acetrizoate was injected as in series 2. Finally, in a fourth series (Fig. 25*d*) a second dose of thorotrast was injected. The time interval between the injections was 10 minutes. From the roentgenograms it seems obvious that the sodium acetrizoate produces a considerable dilatation of the vessels. A small amount of sodium acetrizoate can be utilized to obtain maximum dilatation of the vessels, and following this, the diagnostic dose of a less toxic contrast medium may then be injected.

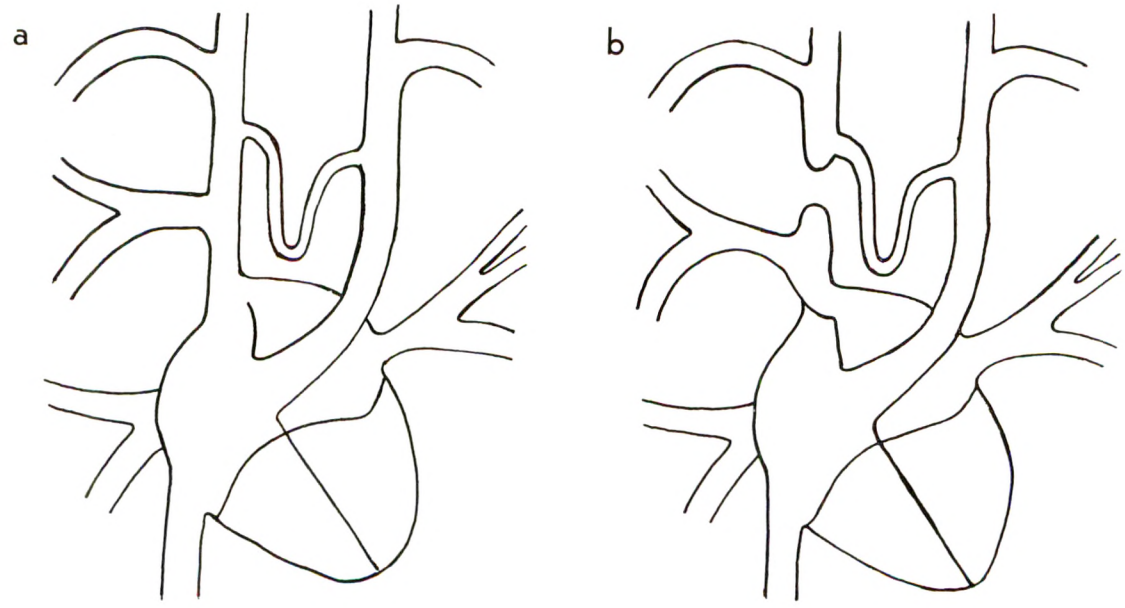


FIG. 24. Schematic drawings of the circulation in the patient illustrated in Figure 22 and 23. (*a*) Before operation. (*b*) After surgical correction.

Hypotension produced over a short period often proves useful in arteriographic studies of the kidneys (Fig. 26, *a* and *b*). At a blood pressure level of around 70 mm. Hg, the filtration pressure is critical for the kidneys. If the blood pressure is reduced to 70 mm. Hg or lower with drugs or by other methods, improved nephrograms can be obtained when the contrast medium passes through the renal vessels.[29] This often facilitates or may even provide conclusive evidence in the assessment of pathologic changes in the kidneys.

Pinet[37] and others have demonstrated

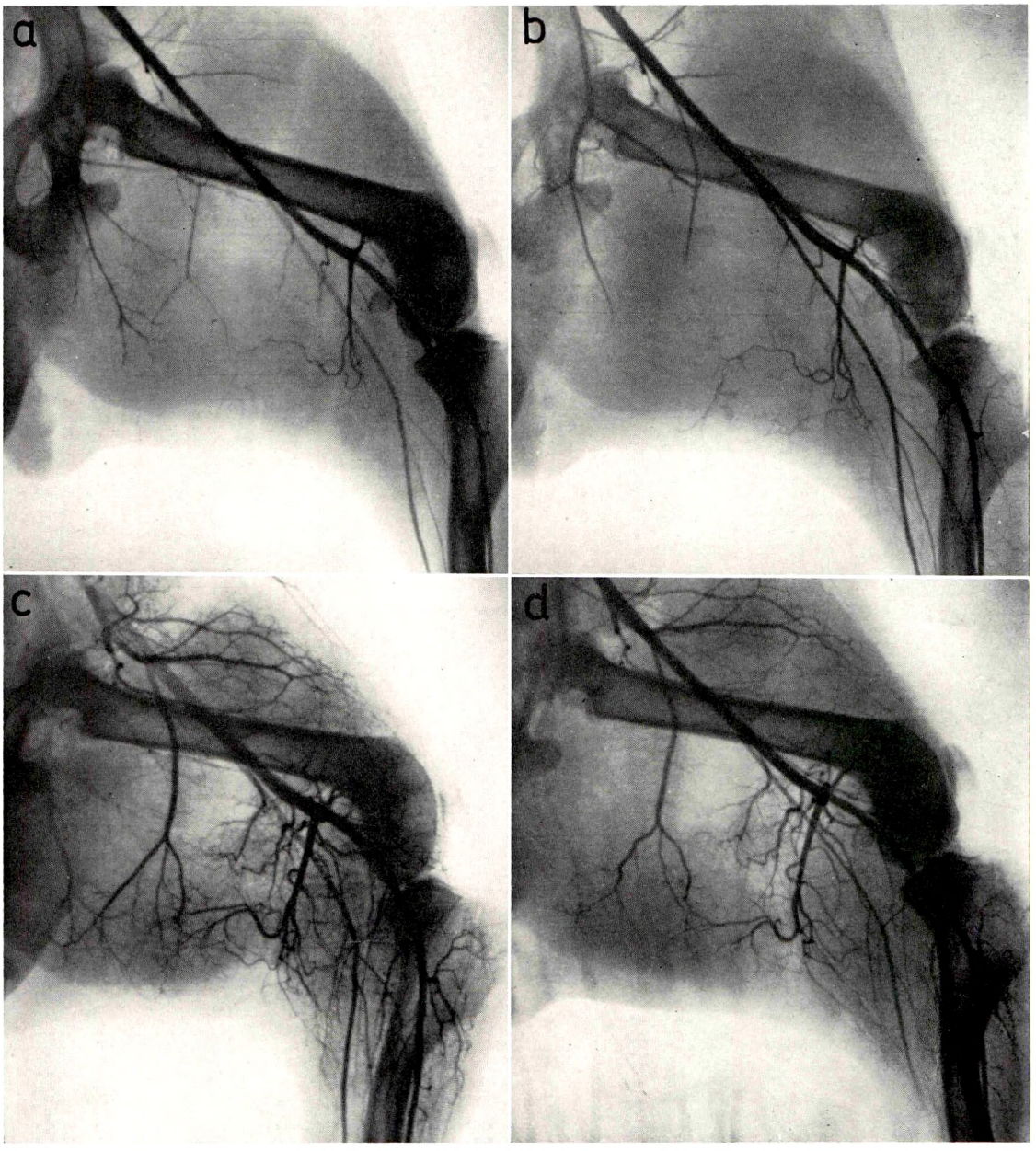


Fig. 25. The effect of sodium acetrizoate (rheopak) upon the femoral arteries in a dog. (*a*) Selective injection of 0.5 ml. per kg. of body weight of thorotrast. (*b*) The corresponding maximum contrast filling after injection of 0.5 ml. per kg. of body weight of a 76 per cent solution of rheopak. (*c*) Second injection of the same amount and concentration of rheopak as in *b*. (*d*) Second injection of the same amount and concentration of thorotrast as in *a*. There was an interval of 10 minutes between the four injections.

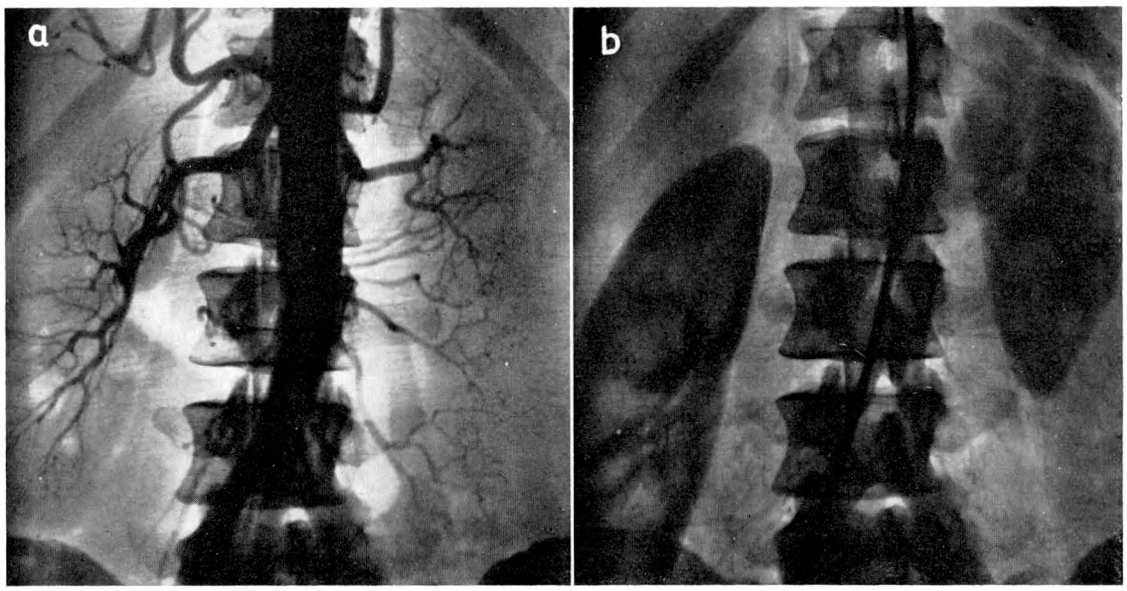


FIG. 26. (*a* and *b*) Renal angiograms showing (*b*) improvement of the nephrographic effect when the blood pressure is lowered.

that in hypotension produced artificially with arfonad, for instance, arterial branches can readily be filled backwards with injection of contrast medium.

Among other chemical agents that have chiefly been used in recent years, special mention may be made of acetylcholine.[1] The idea underlying this method is that, as a consequence of the diminished flow during a temporary cardiac arrest, less dilution of the contrast medium will occur. Arnulf and Chacornac,[1] and several later investigators, have shown that the technique for visualization of the coronary arteries can be improved along these lines. The method is being used in several parts of the world for coronary angiography in man, but it has been criticized by some workers as being not entirely free from risks.

CONCLUSION

From the examples mentioned here of how the circulation may be influenced mechanically or chemically in contrast examinations of the cardiovascular system it is evident that many variations in technique are already available. Rapidly expanding possibilities lie before us, and we can without doubt look forward to many important and valuable contributions in this field of diagnostic radiology.

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THE ROENTGENOLOGIC ASSESSMENT OF THE DEGREE OF LEFT-TO-RIGHT SHUNT IN SECUNDUM TYPE ATRIAL SEPTAL DEFECT*

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ALTHOUGH there appears to be little doubt that the increased pulmonary blood flow associated with most cases of atrial septal defect can manifest itself by a change from normal in the plain chest roentgenogram, there is by no means agreement as to whether a quantitative correlation exists between the physiologic and roentgenologic parameters. Healy *et al.*[10] in 1949, after studying the roentgenologic changes associated with differing pulmonary hemodynamic states, concluded that above a certain level increases in pulmonary arterial flow produced a proportional change in the roentgenologic appearance of the pulmonary arteries. Campbell[3] arrived at a similar conclusion.

However, in 1955 Kraemer *et al.*,[11] after comparing the roentgenologic and physiologic changes in 20 cases of secundum type atrial septal defect, concluded that no quantitative correlation existed. Specifically, they found no positive correlation between the pulmonary index on the one hand and the degree of vascularity of the lung fields and heart size as assessed roentgenologically on the other.

It is the purpose of this paper to show that by using a somewhat different approach from the usual in interpreting chest roentgenograms of patients with secundum type atrial septal defects, we have been able to predict with reasonable accuracy the size of the left-to-right shunt as determined by cardiac catheterization in the majority of cases.

MATERIAL AND METHODS

The routine 6 foot chest roentgenograms made with held inspiration in the erect posture of 77 patients with secundum type defects proved by catheterization were examined. Only roentgenograms of good quality were accepted and the posteroanterior studies were used throughout. The lateral view was occasionally used if there was difficulty in interpreting the posteroanterior roentgenogram. All cases had had pulmonary blood flow and shunt measurements calculated by the Fick principle. The estimation of the magnitude of the left-to-right shunt in atrial septal defect is extremely difficult because of the uncertainty in determining the mixed venous saturation. To calculate systemic flow, mixed venous saturation was assumed to be a mixture consisting of one-third superior vena caval saturation and two-thirds inferior vena caval saturation.

Estimations of the left-to-right shunt were also made in the majority of patients from systemic dye dilution curves following injection into the pulmonary artery as described by Carter *et al.*[4] and these estimates agreed within 15 per cent of those based on the saturation data. The final figure for the percentage left-to-right shunt as determined at cardiac catheterization was taken as the average of the two estimates. To simplify the expression of the results, the shunts were expressed as a percentage of pulmonary blood flow and not in terms of liters per minute or pulmonary indices.

The roentgenograms were read by 3 of us independently and the procedure was conducted as a blind trial. In the majority of cases, good agreement between the 3 observers was found; however, where the

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observations were discordant, roentgenograms were reviewed by the 3 of us together. Thirty control chest roentgenograms of patients in whom it was known that an increase in pulmonary flow was absent were included in the series.

The roentgenograms were read in the following manner.

All cases of severe pulmonary hypertension were first excluded by comparing the markedly enlarged main pulmonary artery shadow, the widened pulmonary artery branches and the narrowed peripheral arteries. This was readily and consistently achieved in 8 of the 9 patients. Assessment of the size of the shunt in these cases was not attempted.

The lung fields of the remaining cases were divided into 6 zones—upper, middle and lower on the right and the same on the left. The zoning was carried out on a vascular basis; the proportion of the lung fields containing vessel shadows passing predominantly upwards were termed upper zone (U.Z.), the portions containing vessels lying predominantly horizontally being mid zone (M.Z.) and those with the vessels pointing mainly downwards being lower zone (L.Z.) (Fig. 1).

Bearing in mind that there is a gradation of vessels from apex to base, with the basal vessels normally far more prominent than the apical (*vide infra*), the degree of plethora had to be assessed in each zone separately. Since the upper and mid zones do not normally display prominent vessels, a small degree of upper or mid zone plethora could be assessed with some degree of objectivity. Greater difficulty was experienced in the lower zones where vessels are normally more abundant; plethora, however, could be recognized in several ways. Simple widening of the vessels was most common; at times the number of small vessels in a given area appeared greatly increased and occasionally in very large shunts the periphery of the bases assumed a feathery appearance. Each zone was graded as follows: If there was no plethora in a zone, the grading was zero (0); if plethora was doubtful,

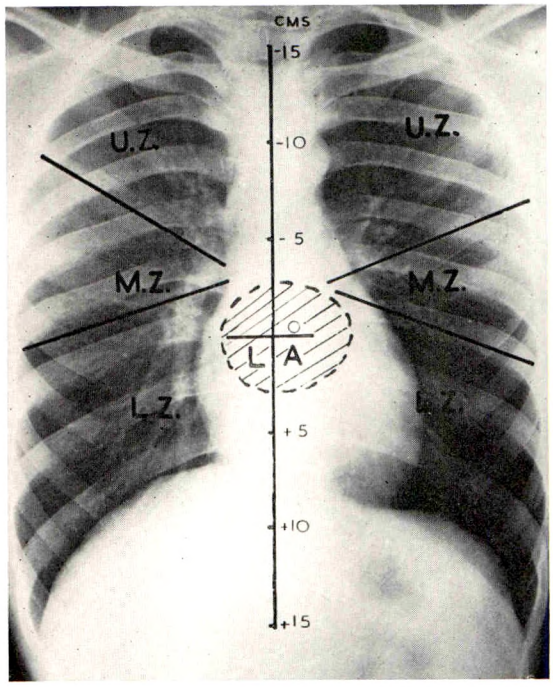


Fig. 1. Erect chest roentgenogram of a normal subject demonstrating the gradation in the width of the pulmonary vessels from apex to base. An indication is given of the way the lung field is divided into 6 zones in relation to the direction of the vascular markings. The difference in hydrostatic pressure between apex and base is also illustrated.

the grade was questionable (Q); and if plethora was present in the upper or mid zones, whether this was mild, moderate or gross, a grading of one plus (+) was given. In the lower zones, however, distinction was made between plethora which was designated as + and gross plethora which was designated as ++. If, as happened on occasion, the left lower zone was markedly obscured by the heart shadow, the symbol NS (not seen) was used. This is demonstrated in Figures 2–4.

To express these results graphically, numerical scores were allotted to each zonal grade and, by adding the individual scores together, the total number of zone units was obtained. Thus, a grade of zero was given a score of zero; the grade Q was given a score of half; grade + was given a score of one and grade ++ was given a score of two. The symbol of NS was given

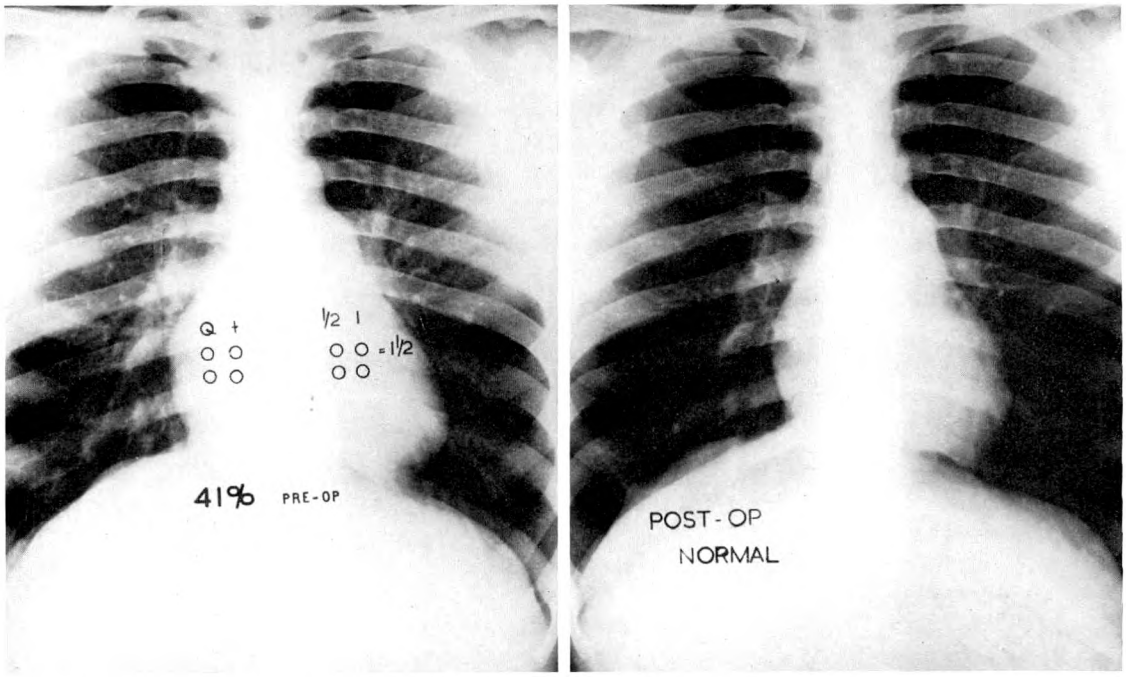


FIG. 2. Chest roentgenograms of a patient with a secundum defect and a small 41 per cent left-to-right shunt. Slight upper zone plethora is shown and is emphasised by the normal appearance after successful surgical closure of the defect. The method of grading the plethora and assessing a numerical score is indicated.

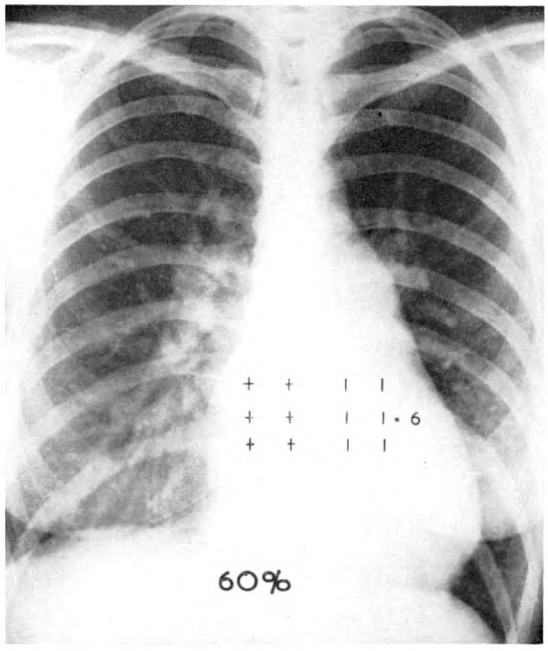


FIG. 3. Chest roentgenogram of a patient with a secundum defect and a moderate 60 per cent left-to-right shunt. Notice that plethora is present in the upper middle and lower zones. The grading and score are indicated.

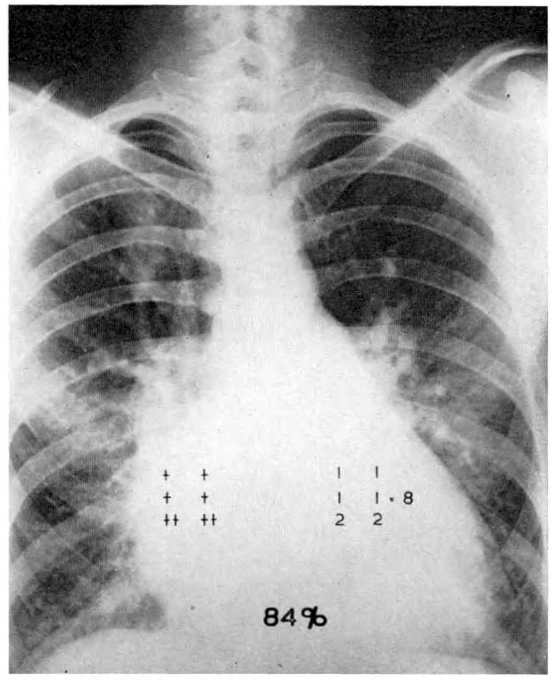


FIG. 4. Chest roentgenogram of a patient with a secundum defect and a large 84 per cent left-to-right shunt. Gross plethora is present in the lower as well as the upper and mid zones. The grading and score are indicated.

the same score as the contralateral zone.

The cardiothoracic ratio was also measured on each roentgenogram.

RESULTS

The results of the present investigation are shown graphically in Figure 5. It will be noted that of the 30 control roentgenograms 2 were assessed as having a small degree of pulmonary plethora. This plethora was of the upper zone type and it was of interest that both patients were infants in whom the usual gradations from apex to base are known to be small. Of the 9 cases with pulmonary hypertension, only 1 was assessed as having pulmonary plethora without signs of high pulmonary artery pressure.

If all patients with a shunt flow of less than 50 per cent are considered (Fig. 5), it will be seen that except for 4 cases all have a zonal score of 4 or less. Of all the patients with a shunt of 50 per cent or more, only 3 had a zonal score below 4 units. On the other hand, when the maximal assessment of 8 units was scored, all had a percentage shunt of 70 or over except for 3 patients, 1 of whom had a shunt in the high sixties and another had mitral stenosis (Lutembacher's syndrome).

An important feature which arose from the investigation (which has not been indicated in the figures) was that, with 1 exception, all cases showing pulmonary plethora demonstrated this in the upper zone. In addition, if lower zone plethora was present, then the mid zone as well as the upper zone was affected.

It is evident from Figure 5 that uniform accuracy was by no means obtained, but a certain trend could be determined. Thus, in a known case of secundum defect if plethora is absent or limited to the upper or mid zones, the shunt will probably be below 50 per cent, whereas if plethora is present in all zones the shunt will probably lie above 50 per cent. Furthermore if gross plethora is present in the lower zones, the shunt will

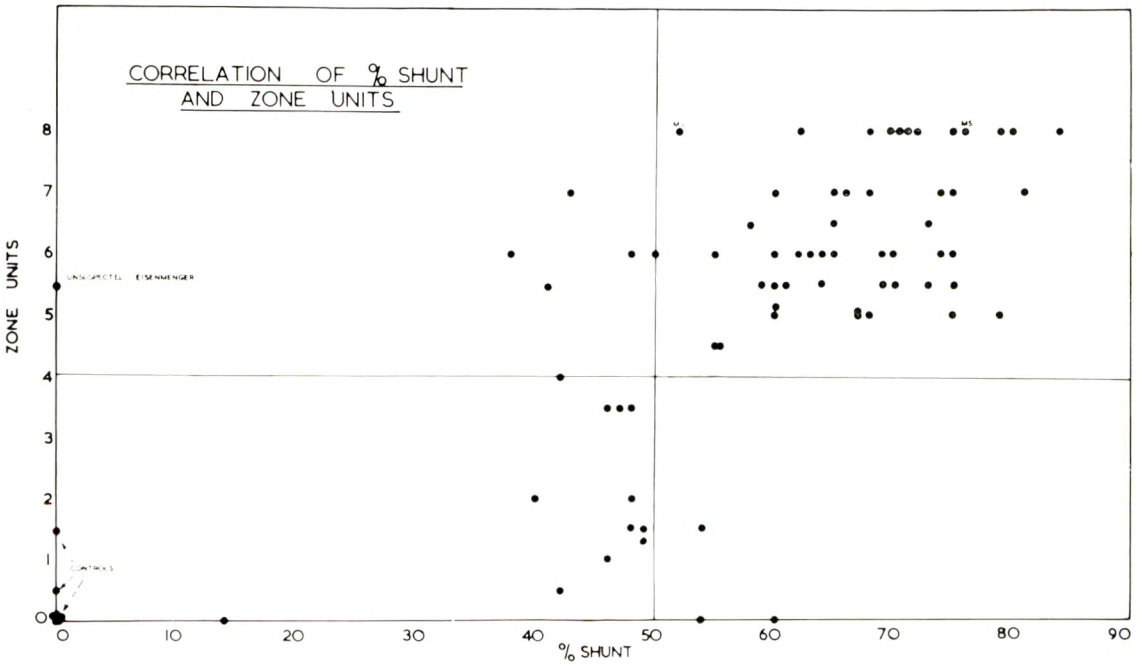


Fig. 5. This shows the results of graphically plotting the zone units against the percentage left-to-right shunt in 69 cases of secundum defect. Eight cases with marked pulmonary hypertension are not included, as they were correctly assessed. All scores below 4 (marked by the horizontal line) indicate that if plethora was present it was seen only in the upper, or upper and mid-zones.

probably be very large—in the 70 to 80 per cent range.

If the cardiothoracic ratio is plotted against the percentage left-to-right shunt (Fig. 6), a rough correlation can be seen.

DISCUSSION

The above results show that in this series of patients there appears to be a definite relationship between pulmonary blood flow expressed as percentage shunt and pulmonary plethora as assessed from the chest roentgenogram by the above method.

The roentgenologic parameters most usually assumed to bear some relationship to increased pulmonary flow are heart size and the generalized increase in width of the pulmonary vascular markings, often termed pulmonary plethora. This latter sign must be clearly distinguished from the distended vessels and interstitial congestive changes produced by the high pulmonary venous pressure unassociated with increased pulmonary blood flow. It must also be distinguished from the prominent widening of the proximal segments of the pulmonary arteries in pulmonary hypertension.[8,9,12]

It has been our experience that the roentgenogram of the normal healthy chest made in the erect posture shows a gradation in the width of the pulmonary vascular markings from apex to base (Fig. 1). The vessels at the apex are narrower than those at the base. This normal pattern, which is readily upset by the presence of either pulmonary or cardiovascular disease, may be due to the difference in hydrostatic pressure between apex and base.[5] If it is assumed that the pulmonary vessels behave even partially as elastic tubes, then it is evident that since the transmural pressure or distending force becomes greater as the base is approached, the caliber of the vessels in the lower zone would be proportionately greater than in the mid or upper zones.

A further point arises; namely, that it might be expected that the blood flow through the apices would be less than that

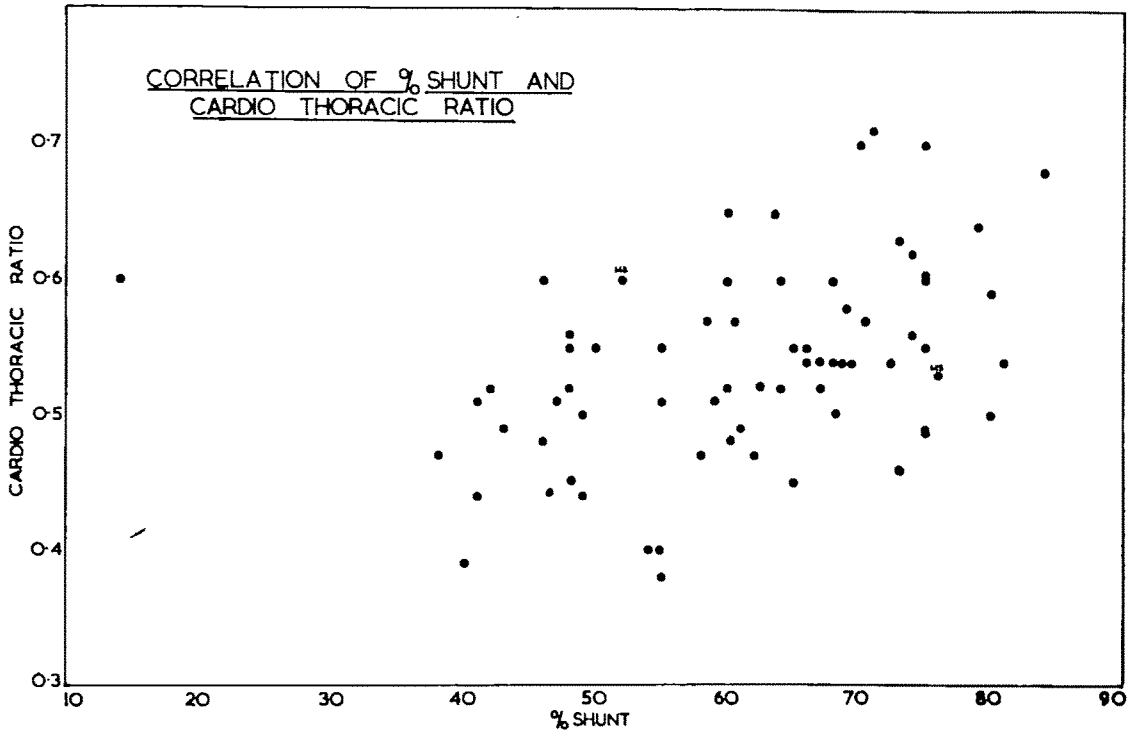


FIG. 6. The results of graphically plotting the cardiothoracic ratio against the percentage left-to-right shunt in the series of cases under investigation are shown. A rough correlation appears to exist.

through the bases. The reason for this is that since the caliber of the apical vessels is less than at the bases, the resistance offered to flow through the apical vessels will be higher and the flow through them will, as a consequence, be less.

The above arguments will, of course, be rendered invalid if the patient assumes the horizontal position and should apply with less certainty in the small chest of the infant or young child where hydrostatic pressure differences between apex and base are considerably less than in the adult.

Some of the implications of the aforementioned statements have been substantiated over the last few years in experiments carried out by the group at Hammersmith[6] in which regional pulmonary blood flow has been measured with the use of a radioactive oxygen and carbon monoxide technique.[6,7,13]

If increased blood flow is to be accommodated in the lungs with minimal change in pulmonary artery pressure as in cases of atrial septal defect, the partially collapsed vessels in the apex would seem to offer the most ready potential pathway. Furthermore, if the mean pulmonary artery pressure is normal and the critical closing pressure concept of Burton[1] is accepted, there will probably be many totally collapsed arteries in the apical regions. For example, if the mean pulmonary artery pressure is assumed to be 10 mm. Hg and the hydrostatic drop to the apex is 6 mm. Hg, then the transmural pressure in the apical vessels will be 4 mm. Hg, a level below which critical closing should occur.[2] Thus, in the erect posture the potential ability of the pulmonary vasculature to dilate in order to permit higher blood flows might be considered to be greatest at the apex and least at the base and intermediate in the mid zones. Theoretically, therefore, small shunts should produce plethora in the upper zones only, while large shunts should produce plethora throughout the lung fields.

The results of our investigation tend to support this hypothesis, and it would seem that the implication of changes in regional pulmonary blood flow in conditions of left-to-right shunt, recently demonstrated by the Hammersmith group,[6] may have some relevance in the interpretation of chest roentgenograms of patients with these conditions. It must be stressed, however, that by basing this investigation on nonhypertensive secundum type defects, theoretically, the best material for observing flow changes in the absence of pressure changes was chosen.

It is of some interest to note that if our observations are valid then the pulmonary vasculature as demonstrated on the chest roentgenogram is not only of value in the assessment of pulmonary arterial and pulmonary venous pressure but is also a semiquantitative indicator of flow changes in the absence of marked pulmonary arterial or venous pressure changes. The results shown in Figure 6 indicate that heart size as expressed by the cardiothoracic ratio should provide a further help in the assessment of pulmonary blood flow in this condition. Although we had assumed empirically in the past that heart size and pulmonary blood flow were related, nevertheless our findings appear somewhat unusual in view of the results obtained by Kraemer *et al.*[11]

From the practical point of view, we have found the sign of localized upper zone plethora to be of some value in the diagnosis of small atrial septal defects. Furthermore, the division of the percentage shunt into above or below 50 per cent, depending upon the presence of localized or generalized plethora, has in our experience likewise proved of some value. It should be noted, however, that small degrees of upper zone plethora appear to be difficult or impossible to assess in infants, owing to the lack of normal gradation of vessel size from apex to base.

SUMMARY

1. A hypothesis has been advanced which suggests the possibility of distinguishing between small and large left-to-right shunts on chest roentgenograms of patients with atrial septal defect.

2. The results of an investigation based on this hypothesis have been presented and tend to confirm this hypothesis.

3. It appears that small shunts are characterized by the presence of upper or mid zone plethora, whereas in large shunts plethora is present throughout the lung fields.

4. A direct correlation between the size of a left-to-right shunt and heart size as expressed by the cardiothoracic ratio also appears to exist.

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THE USE OF CORONARY CINEARTERIOGRAPHY FOR ESTIMATION OF THE RELATIVE FLOW IN THE ANTERIOR DESCENDING CORONARY ARTERY IN DOGS AFTER EXPERIMENTAL SURGICAL CONSTRICTION*

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IF A surgical procedure which is intended to stimulate the development of collateral arterial channels from an extracardiac source to the coronary arteries is to be soundly designed,[3] it seems wise to understand thoroughly the basic physiologic factors related to the development of collateral arteries. Experiments were performed in an effort to clarify the relationships between pressure, flow, velocity, and lumen size in the anterior descending coronary arteries of dogs before and after experimental surgical procedures.

Although brilliant advances have been made in the technique of electromagnetic measurement of flow, a roentgenographic method was selected as the most practical approach for obtaining useful information about abnormalities in flow and velocity in the anterior descending artery after surgical constriction. Angiographic techniques for estimation of flow are not new.[1,2] This method permits study of a postoperative dog with the chest closed with minimal interference with the experimental conditions.

EXPERIMENTAL DESIGN

The experimental design is based on the fact that flow through a cylindrical conduit is related to the cross-sectional area of the lumen and the velocity of movement through it.

The relative size of the postoperative anterior descending artery was obtained as follows: Coronary arteriograms were taken using a cinefluorographic technique.[4] At subsequent thoracotomy the pressure was monitored in the distal anterior descending artery and the proximal end of this artery was constricted by twisting a wire until the desired pressure changes were obtained. Several hours to several days later, arteriography was repeated, using a comparable technique. The size of the distal anterior descending artery was compared to that of the circumflex in the preoperative arteriogram and a similar comparison was obtained from the postoperative roentgenograms. The size of the distal postoperative anterior descending artery could then be expressed as a percentage of normal.

The relative velocity of movement in the anterior descending artery was determined in a similar manner. The rate of advance of the column of radiopaque medium in that artery was compared with the rate in the circumflex on the preoperative and the postoperative arteriogram. Comparison of these values permitted expression of the postoperative velocity as a percentage of normal.

Calculations from these data permitted the amount of flow in the anterior descending artery relative to the circumflex of the postoperative dog to be expressed as a percentage of normal for that dog. Absolute values for flow in cubic centimeters per minute could not be obtained by this method, but it was not necessary for the purposes desired.

ROENTGENOGRAPHIC EQUIPMENT AND TECHNIQUE

The roentgenographic equipment and technique have been recently described in

* From the Veterans Administration Hospital, Oteen, North Carolina.
Presented as an exhibit at the American Roentgen Ray Society Meeting, Miami Beach, Florida, September 26–29, 1961.
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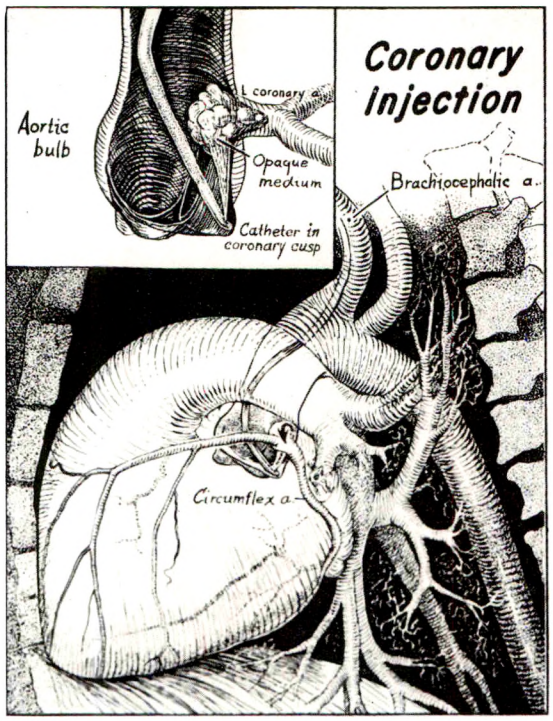


Fig. 1. Position of the catheter for coronary arteriography used in this study.

detail.[4] Apparatus made by the Picker X-Ray Corporation was employed. Technical factors included the use of an 8 inch image amplification tube, a 35 mm. Plus-X film, a 0.5 mm. focal spot roentgenographic tube with a triple speed rotor, roentgenographic magnification, exposure of each frame for 1/200 of a second, 30 frames per second, and Eastman D11 developer.

A radiopaque polyethylene catheter was inserted through the carotid or femoral artery of the dog and the tip was positioned in the sinus of Valsalva with fluoroscopic control (Fig. 1). The tip of the catheter was closed, and the single hole near the end was positioned to direct the jet of medium directly toward the orifice of the coronary artery. Direct catheterization of the coronary artery was avoided for fear of artificially altering the relationships between flow in the major branches.

Ten or 15 cc. of warm 90 per cent hypaque was injected at a pressure of about 30 lb. per square inch. The injection continued over about 6 cardiac cycles. Filming was done in the left lateral position.

Calculation of the Relative Lumen Area

The change in cross-sectional lumen area of the distal anterior descending artery between the pre- and postoperative studies was calculated. For this work, a standard 35 mm. movie editor was used.

A corresponding frame was selected from each arteriogram. The frame used was the last one before the onset of systole in the first diastole after maximal filling of the coronary arteries had occurred. A point on the anterior descending artery was selected and its relationship to branches was carefully noted. The diameter was carefully measured by placing the points of a needle caliber in the center of the penumbra on each side of the anterior descending artery (Fig. 2). This distance was measured to the nearest 1/1,000 of an inch, using a machinist's micrometer. The diameter of the circumflex was measured in a similar manner. Comparable measurements were taken from the corresponding frame in the postoperative arteriogram (Fig. 3).

Each diameter was squared, giving the cross-sectional area for that artery multi-

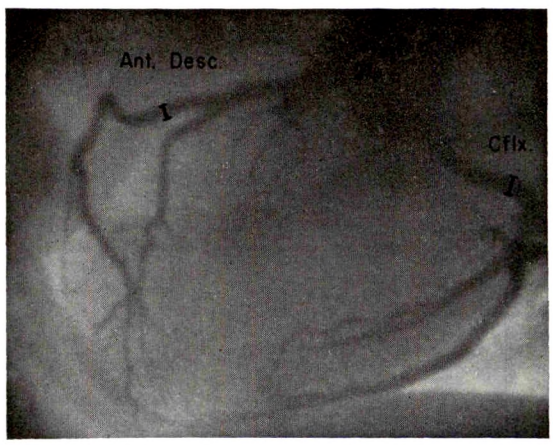


Fig. 2. The frame selected from the preoperative coronary cinearteriogram. The diameters of the anterior descending artery and the circumflex were measured as indicated. Reproduced from a 35 mm. film.

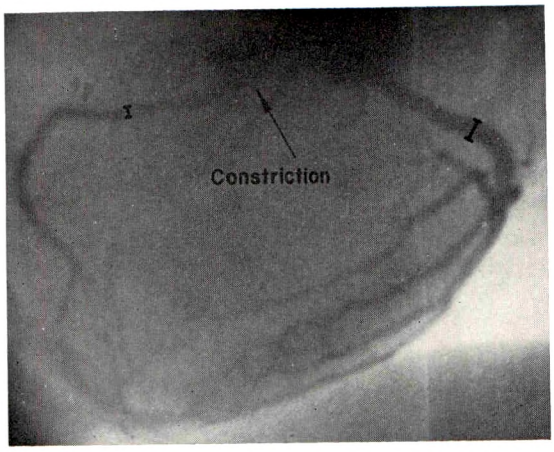


Fig. 3. A comparable frame from the postoperative arteriogram of the same dog as shown in Figure 2. The anterior descending and circumflex arteries were measured at comparable points. The large branch arising from the anterior descending artery just proximal to the point of measurement in Figure 2 is partly obliterated in this frame because it was sacrificed at the time of thoracotomy for pressure measurements.

plied by an unknown constant factor. This expression for the lumen area of the anterior descending artery was divided by the one for the circumflex, thus cancelling out the unknown factor. The quotient expressed the ratio of the cross-sectional lumen area of the anterior descending artery compared to that of the circumflex, and was written as a decimal.

A similar ratio was obtained from the postoperative study. This postoperative ratio was divided by the preoperative one, giving the percentage of the normal cross-sectional area of the distal anterior descending artery that was present at the time of the postoperative study.

The standard deviation of the experimental error was determined, because of the difficulty in obtaining the measurements precisely. Arteriograms were taken on 4 separate days on the same normal dog, and the proper frame was selected and the vessels were measured 10 times from each arteriogram. The standard deviation of the ratios was about 5 per cent (Fig. 4). This means that if 10 measurements are made from a preoperative arteriogram and averaged, then a ratio obtained from a single postoperative measurement which differs by more than 10 per cent from the preoperative average is significantly different at the 0.05 level. A similar value which represented an average of repeated measurements from the postoperative arteriogram would, of course, have greater significance.

Calculation of Relative Velocity

The percentage of normal velocity of the movement of medium in the anterior descending artery of the postoperative dog was estimated by comparing the distance filled in the postoperative arteriogram with that in the preoperative study, at a time of comparable filling of the circumflex.

To do this, the proper frame was selected from the preoperative study. This was the first frame that showed maximal filling of the anterior descending artery. The distance was measured from the apex to the closest point of opacification of the anterior descending artery, or one of its major distal branches. Also measured was the distance from the apex to the closest point of filling from a branch of the circumflex, and the distance from the apex to the closest point of the aortic valve.

In the postoperative study, the frame

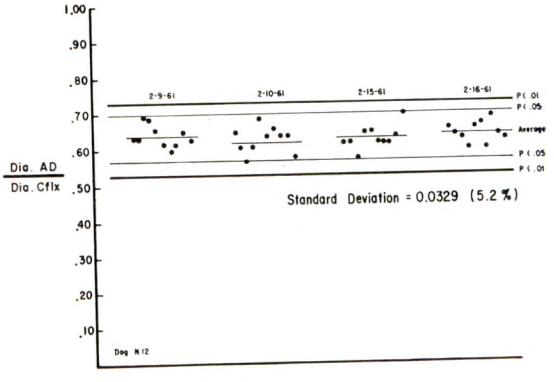


Fig. 4. The standard deviation of repeated measurements of the ratio of the diameter of the anterior descending artery to the diameter of the circumflex. Arteriograms were taken on 4 separate days on the same normal dog and measurements were made 10 times from each arteriogram.

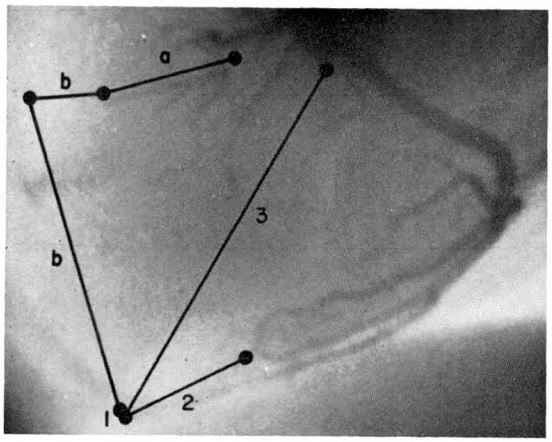


Fig. 5. The frame from the postoperative study that was used for velocity calculation. It was compared with a frame earlier than Figure 2, but similar to it. The distances measured were (1) from the apex to a point corresponding to the closest opacification of the anterior descending artery in the preoperative study, (2) from the apex to the closest opacification from the circumflex, (3) from the apex to the aortic valve, (a) the distance from the distal opacification of the anterior descending artery to the proximal end of the filling defect caused by the surgical constriction, and (b) the unopacified route which the anterior descending artery would have been expected to follow if it had been normal.

was selected that had the distance from the apex to the closest filling from the circumflex, divided by the distance from the apex to the aortic valve, equal to the ratio of these distances obtained from the preoperative study (Fig. 5). In this manner, the single frame with filling of the circumflex comparable to that in the frame from the preoperative study was located.

The distance from the filling defect caused by the surgical constriction of the proximal anterior descending artery to the distal limit of opacification of that artery in the postoperative frame was divided by the distance that it would have been expected to fill if the dog had been normal, as calculated from the preoperative frame. This gave a figure which expressed roughly the postoperative velocity in the anterior descending artery as a percentage of normal.

The measurements used in the velocity study were of the order of centimeters, rather than thousandths of an inch. They therefore could be repeated with very little variation. However, this calculation was subject to more intrinsic geometric errors than the one used for the lumen area.

CALCULATION OF FLOW

The percentage of normal flow in the anterior descending artery of the postoperative dog was calculated by multiplying the percentage of normal cross-sectional lumen area times the percentage of normal velocity.

CORRELATIONS BETWEEN OBSERVATIONS

Studies were done on 16 dogs before and after surgical constriction of the proximal anterior descending artery. There were 6 postoperative dogs with normal velocity and a decreased lumen size, but none with a normal lumen and a decreased velocity (Fig. 6). Apparently, a mild constriction resulted in a decrease in the lumen size but caused no change in the velocity. The dogs with a tighter constriction had a decrease in both the lumen size and the velocity. There was wide variation in the relationship between these two.

Pressure was monitored in the distal an-

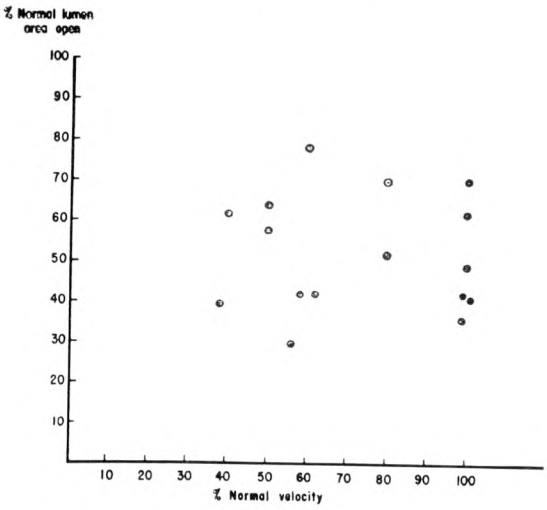


Fig. 6. The percentage of normal cross-sectional area of the lumen of the distal anterior descending artery of postoperative dogs versus the percentage of normal velocity of movement of medium in the anterior descending artery.

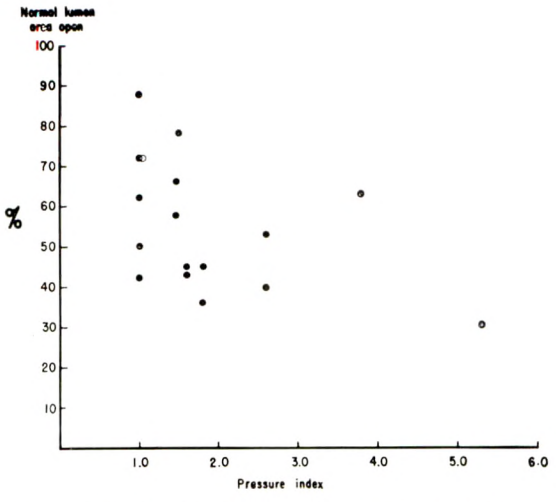


FIG. 7. Relationship between the percentage of normal distal lumen area as used in Figure 6 and the index of hypotension in the anterior descending artery distal to the surgical constriction. An index of 1.0 means normal pressure, and 6.0 means severe hypotension.

terior descending artery at the time of surgery, and was measured in some dogs postoperatively. Polyethylene catheters were inserted into a branch of the anterior descending artery and into a systemic artery for these studies. An index of hypotension was developed in order to incorporate mathematically the many variables present in the pressure measurements, and to permit comparisons between dogs. This index consisted of the initial coronary systolic pressure minus the coronary diastolic pressure after completion of the operation, divided by the initial coronary pulse pressure, after appropriate corrections for changes in the aortic pressure. This formula was selected from many tested because of theoretic considerations and the fact that it gave the best correlation with the size of intercoronary collateral channels which were found in corrosion casts made after autopsy of the dogs. An index of 1.0 meant a normal pressure in the distal anterior descending artery and 6.0 represented severe hypotension.

There was a certain amount of correlation between the percentage of normal lumen area open and this index of hypotension (Fig. 7). There were no dogs with normal lumen area and reduced pressure, but there were some with normal pressure and reduced lumen. In other words, mild constrictions were followed by a decrease in the distal lumen size, but did not lower pressure.

There was also a general correlation between the percentage of normal velocity and this index of hypotension (Fig. 8). There was no clear-cut distinction between the effect of a mild constriction on the velocity and its effect on the pressure. In general, a very mild constriction seemed to decrease the lumen size without change in the velocity or pressure. A somewhat tighter constriction reduced the velocity and the pressure without any clear-cut preponderance of the effect on one over the other.

A better correlation was found when the percentage of normal flow in the postoperative dog was compared with the index of hypotension (Fig. 9). In general, the pressure was reduced only in those dogs with flow less than about 50 per cent of normal.

The normal pressure with a decreased flow indicates that the surgical constriction of the anterior descending artery was followed by a spontaneous increase in periph-

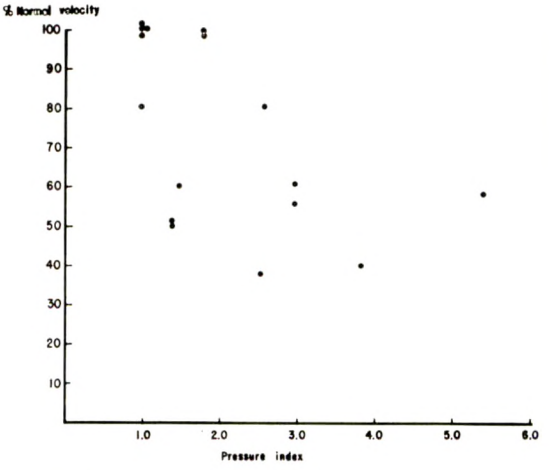


FIG. 8. Relationship between the velocity of movement used in Figure 6 and the index of hypotension used in Figure 7.

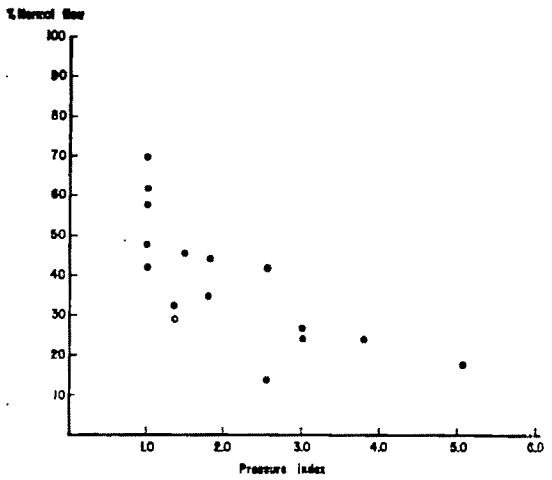


FIG. 9. The percentage of normal flow in the anterior descending artery as calculated from the velocity of movement and cross-sectional area of the lumen versus the index of hypotension.

eral resistance of the artery. This is in agreement with the results of acute experiments in another series in which the flow in the anterior descending artery was continuously monitored by an orifice-type flowmeter. These dogs consistently showed a gradual spontaneous increase in the distal coronary arterial pressure and a simultaneous decrease in the flow for a period of 20 to 30 minutes after the surgical constriction.

In chronic experiments, the pressure was measured in the distal anterior descending artery several days to several weeks postoperatively, and was found to correspond more closely with the pressure at the end of thoracotomy than with pressures taken earlier in the operation.

INFORMATION OBTAINABLE FROM A POSTOPERATIVE STUDY ALONE

Studies were done to find out how much information could be obtained from a postoperative study alone. Figure 10 shows the actual ratio obtained by dividing the diameter of the anterior descending artery by the diameter of the circumflex. When pre- and postoperative arteriograms are available, it is necessary only for the postoperative value to be significantly below the preoperative value to demonstrate a significant change. If only the postoperative arteriogram is available, then the ratio must be significantly below the normal range. This would have occurred in few, if any, of the dogs in this series.

Estimation of the velocity in a postoperative arteriogram by comparison with the normal range, rather than with the preoperative study, appears to include too much chance of error to be of value for mild constrictions. However, it seems very promising for the diagnosis of very severe constriction, judging from the several dogs in this range in the current study.

Further work should be done on more dogs of this type, as this is probably a situation comparable to many clinical problems.

LIMITATIONS OF THE METHOD

There are several geometric factors which introduce unavoidable errors into the calculations presented. The most prominent error appears to be in the velocity calculation and results from the fact that the an-

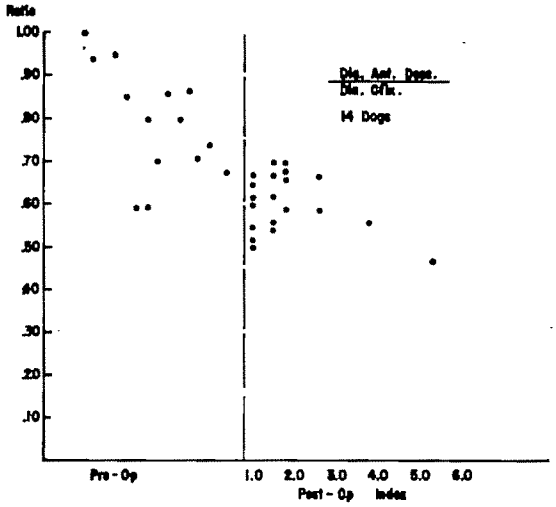


FIG. 10. The absolute ratio obtained by dividing the diameter of the anterior descending artery by the diameter of the circumflex in the pre- and postoperative studies. The degree of abnormality of this ratio in the postoperative dog can be determined only by comparison with the same dog preoperatively and not by comparison with normal range.

terior descending artery is not a perfectly regular cylinder but tapers in a somewhat variable manner. Also, it does not follow exactly the same plane in relation to the plane of the film throughout its course.

Although variations in the degree of roentgenographic magnification might seem to introduce large errors, these are probably minimal because the diameter of the anterior descending artery is compared with the circumflex in the same frame, and each measurement in velocity calculation is compared with the distance from the apex to the aortic valve. Slight variations in position of the dog on the table might result in a proportional magnification of different areas of the heart, but again this would seem minimal.

Hypaque has been shown to change the diameter of coronary arteries of dogs.[5] However, the length of time required for this change was relatively long as compared to the interval between the time of initial filling of the coronary arteries and exposure of the frames used for the current study. This factor was therefore probably a minor one.

The technique was not compared with any other method for measuring flow in the anterior descending artery because of practical difficulties. It appears, however, to be on a solid geometric basis and the potential errors are believed to be small in comparison to the magnitude of changes observed. Otherwise, comparison of the percentage of normal flow with the index of hypotension would have shown much more scatter than is seen in Figure 10.

The technique does not seem to be practical for obtaining information on phasic flow, or absolute values for flow in cubic centimeters per minute. Fortunately, neither is needed for the purposes for which the technique was designed.

POTENTIAL VALUE OF THE METHOD

An extensive study is in progress on basic physiologic factors influencing the development of collateral arterial channels from an extracardiac pedicle to the coronary artery. Studies have shown that the extent of stimulation of collateral development is primarily related to coronary arterial pressure differentials and, indirectly, to needs of the myocardium for additional blood. Function of the heart, mortality, and infarct formation is related more directly to the amount of arterial blood in various regions of the myocardium than it is to coronary pressure.

The method presented has been of tremendous value in understanding the physiologic processes in these experimental animals. This knowledge is necessary for the successful design of an experimental procedure for revascularization of the myocardium, and current trends suggest that it will be essential for selecting patients who have a pathologic and physiologic condition which is potentially amenable to this type of surgical approach.

Furthermore, an understanding of the relationship between diameter, velocity, flow, and pressure in abnormal coronary arteries of dogs will probably be helpful in arriving at a physiologically oriented interpretation of future human coronary arteriograms.

SUMMARY

Coronary hemodynamics were studied by using measurements from 35 mm. coronary cinearteriograms taken at 30 frames per second on dogs. Contrast medium was injected directly into the left sinus of Valsalva.

The relative diameter and rate of movement of contrast medium in the anterior descending artery were measured and compared with the circumflex before and after surgical constriction of the anterior descending artery. After appropriate geometric corrections, the postoperative flow in the anterior descending artery could be expressed as a percentage of the preoperative flow.

The experiment showed that a mild proximal constriction of the anterior descending artery was followed by a decrease in the diameter of the distal artery, with-

out change in the relative velocity within it. A tighter constriction was followed by both a decrease in the diameter and a lower relative velocity.

Hypotension in the distal artery did not occur unless the relative flow was reduced by more than about 50 per cent of the preoperative level. It was consistently found with flow below that.

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SINGLE ARM, PERCUTANEOUS INTRAVENOUS AORTOGRAPHY

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THE history and technique of intravenous aortography and arteriography have been thoroughly described by Steinberg, Finby and Evans,[4] Kincaid and Davis,[2] and others.[3] We are presenting our experience with a single arm large bolus technique, because we feel that this simplified method brings the procedure within the scope of any radiology department.

Since there is no resident staff in the Englewood Hospital Department of Radiology and since the amount of time spent in special procedures is a greater factor in a department such as ours than in the larger more completely staffed Medical Centers, our original aim is to simplify all special procedures. With this in mind, we felt that a single arm injection of 80 to 100 cc. of contrast agent, such as Hypaque-M, 90 per cent,* would produce roentgenograms of diagnostic caliber equal to those achieved by bilateral 40 to 50 cc. injections.

Initially, a glass 100 cc. Robb syringe was used, and satisfactory roentgenograms of the aorta, renal, iliac, and femoral vessels were obtained. Although a manually operated mechanical injector has been substituted for the Robb syringe, special equipment is not a *sine qua non* for obtaining diagnostic studies.

The advantages of a single arm over the double arm injection technique are: (1) less discomfort to the patient; (2) less time spent on the procedure; and (3) one less radiologist involved with its performance.

TECHNIQUE

The method is basically the same as described by Steinberg *et al.*, with a few essential variations. Only one antecubital vein puncture is carried out. We have substituted a rapid cassette changer (Sanchez-Perez seriograph) with serial studies in place of a single, 2 to 3 second Bucky tray exposure, and we employ a special flexible connecting tube† between the syringe and needle.

The average technical factors have been 60 to 70 kv. peak, 80 to 100 mas., with .27 to .34 second exposures, at the rate of one per second film change.

The special large bore, 10 inch long plastic tube connecting the syringe with the needle allows a more facile, bimanual, rapid injection, utilizing either the hand syringe or the mechanical injector. When using the mechanical injector, care should be taken to obtain a smooth acceleration of the lever handle, since too forceful initial thrust can result in rupture of the vein and subsequent extravasation of the contrast agent. Hypaque-M, 90 per cent has been the contrast agent used almost exclusively, as it has been found to provide maximum contrast with maximum safety.

RESULTS

Since September, 1960, we have employed the single arm large bolus technique in 60 cases, using for the most part the manually operated mechanical injector.

Cases of aorto-iliac occlusion and aneurysm, have been readily demonstrated (Fig. 1, 2, 3 and 12). Our results have convinced us that single arm intravenous aortography is the diagnostic procedure of choice in study of the aorta.

Of great interest, however, has been our experience with renal artery stenosis. In 35 patients with hypertension, renal artery lesions have been demonstrated in 10, with confirmation in all 6 patients who came to

* Trademark, Winthrop Laboratories, New York.

† x-361 Special flexible connector for cardiography, Becton Dickinson Co.

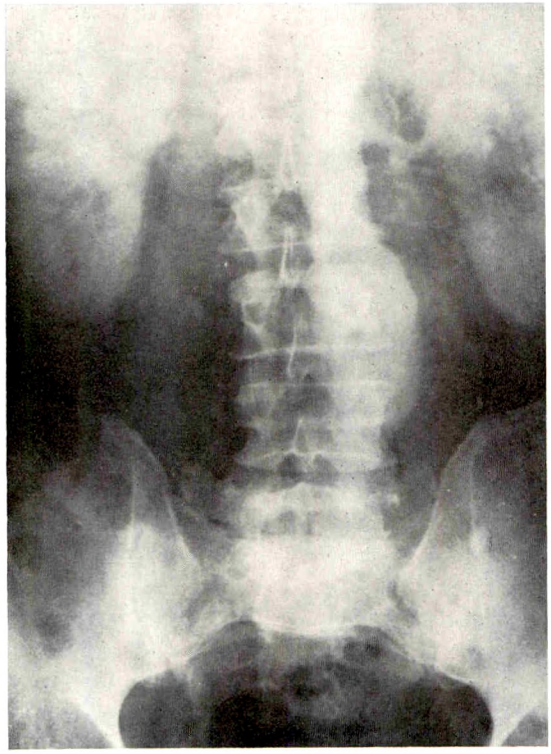


Fig. 1. Case 1. Sixty-five year old male with progressive abdominal pain. Preoperative study reveals a saccular aneurysm. Note the poor demonstration of the iliac arteries. The over-all contrast is not good in this patient but is a phenomenon related to the pathology.

surgery. A variety of obstructing lesions of the renal arteries are shown in Figures 3, 4, 5, 6 and 7. It is apparent that gross lesions with poststenotic dilatation can be diagnosed by means of single arm intravenous aortography. In some cases even minimal plaque lesions have been demonstrated. The authors doubt that intravenous aortography is adequate for detection of all renal artery lesions but recommend its use at least as a screening procedure. It is interesting to note that some authors[3] feel that the best candidates for surgical correction of renal artery stenosis are those patients who manifest poststenotic dilatation. If additional experience supports this viewpoint, intravenous aortography may become a valuable adjunct in the evaluation of renal hypertension.

Several cases were examined by the single arm intravenous technique following corrective vascular surgery. The diagnostic value of the procedure is well demonstrated in Figures 2, 5, 8, 9 and 12.

More recently the technique has been extended to the iliac, femoral and popliteal vessels with excellent results (Fig. 11 and 12). Adequate assessment of the peripheral circulation can be made, avoiding direct femoral artery puncture.

COMPLICATIONS

Local extravasation of contrast material occurred in 3 patients. Two of these were the first cases in which the mechanical injector was used, and the other was a patient with a poor insertion of the Robb-Steinberg needle, in whom the needle was not sufficiently threaded into the vein. Pressure injection should not be done in this event. All 3 patients made an uneventful recovery. It should be emphasized again that extra-

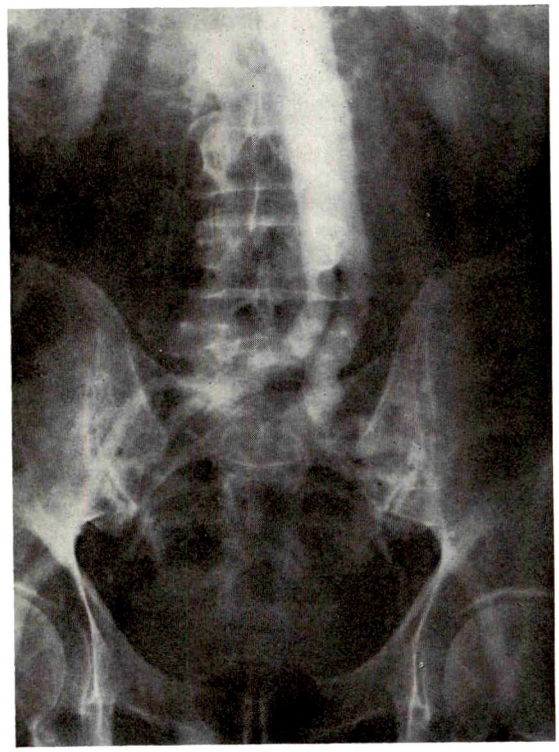


Fig. 2. Case 1. Postoperative study shows the prosthetic graft with excellent demonstration of the iliac run-off.

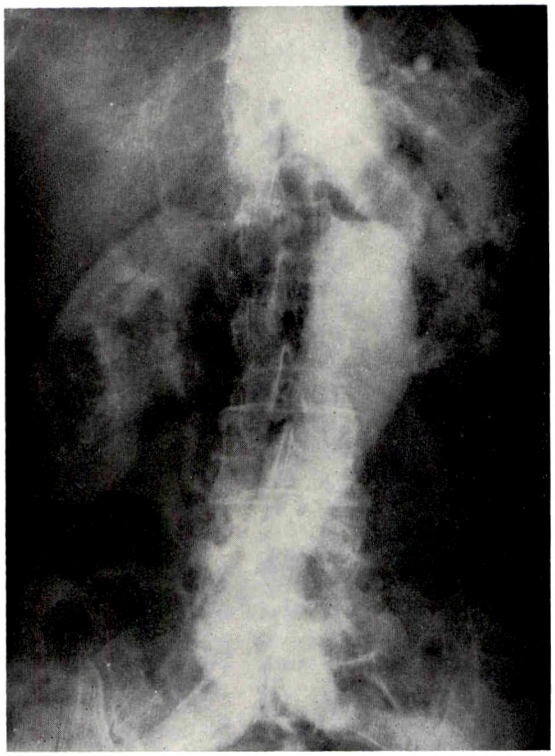


Fig. 3. Case II. Seventy-two year old female with a history of a pulsating abdominal mass of at least 40 years' duration. Coarctation of the abdominal aorta with poststenotic dilatation is demonstrated. Note the huge caliber of the iliac arteries, which supports the hypothesis of poststenotic dilatation. There are arteriosclerotic changes present, but the primary pathology was felt to be congenital.

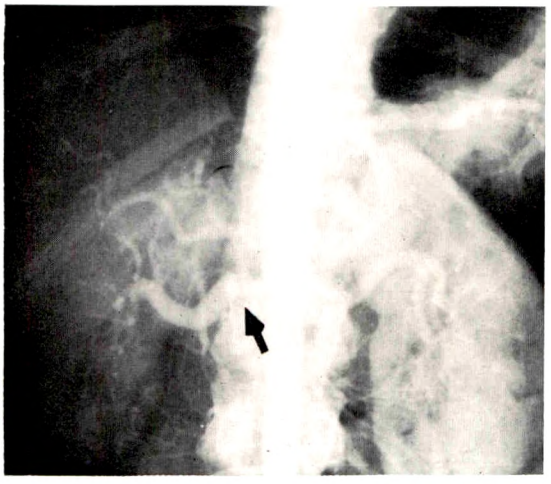


Fig. 4. Case III. Forty-four year old female with hypertension. Preoperative study shows classic stenosis with poststenotic dilatation.

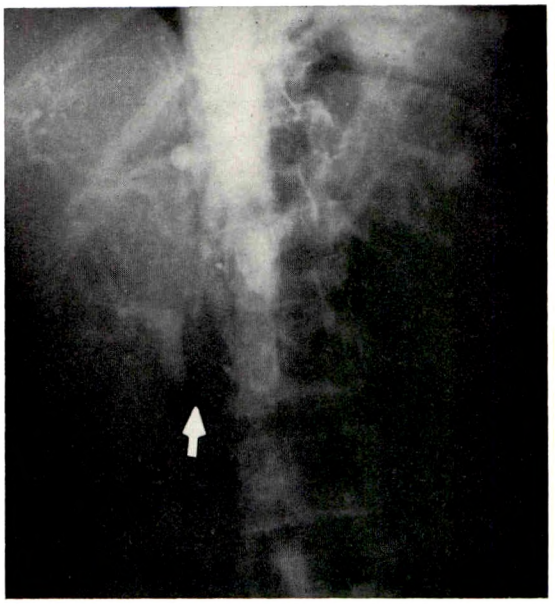


Fig. 5. Case III. Postoperative study following failure of blood pressure reduction shows thrombosis of the bypass graft, confirmed at second operation, with very good short term results following repeat bypass surgery.

vasation can be prevented by a smooth acceleration of the injection speed rather than a sudden energetic thrust with maximum force exerted at the start of injection.



Fig. 6. Case IV. Forty-nine year old patient with hypertension. This study shows stenosis at the origin of a secondary renal artery. Right hemi-nephrectomy was performed with excellent results.

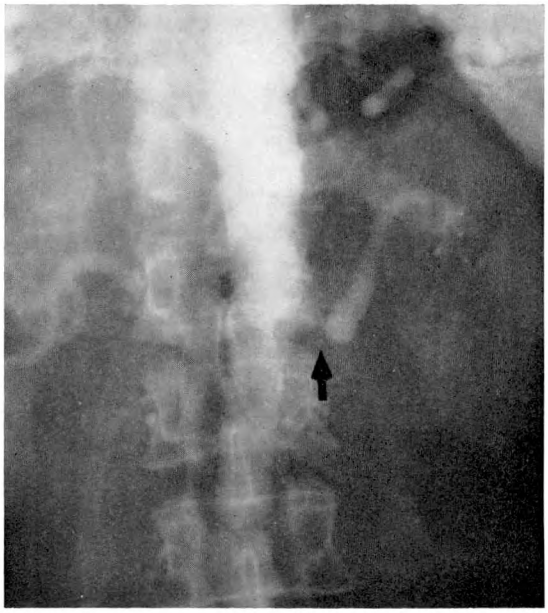


FIG. 7. Case v. Fifty-six year old male with hypertension and severe symptoms. Preoperative aortogram demonstrates stenosis of left renal artery with poststenotic dilatation.

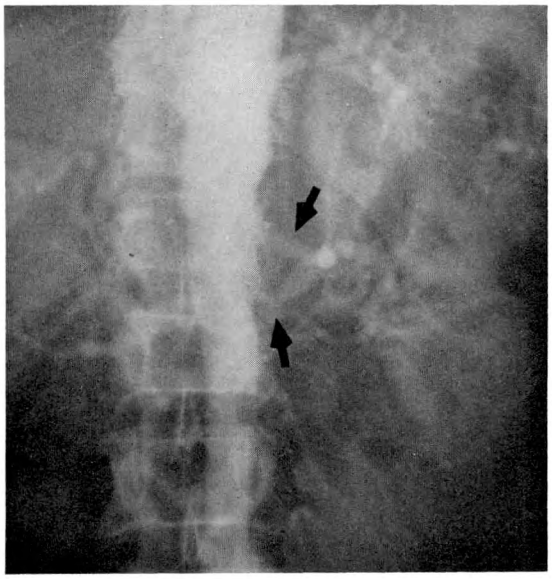


FIG. 9. Case VI. Fifty year old male with hypertension. Postoperative study shows a splenorenal arterial shunt (top arrow). The left renal artery stenosis is demonstrated (bottom arrow).

DISCUSSION

Study of the aorta and its major branches is currently accomplished by means of translumbar aortography, percutaneous

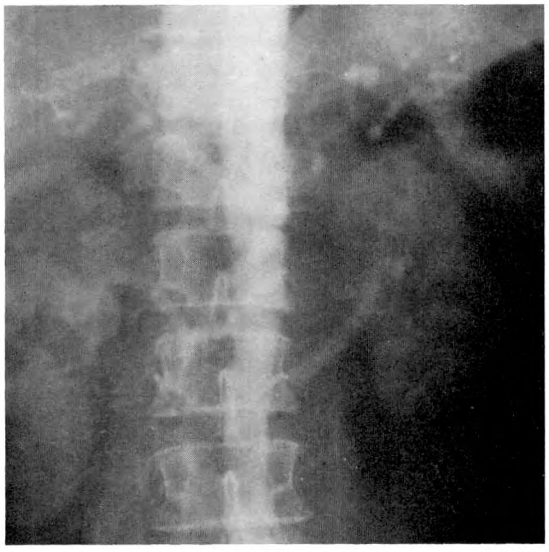


FIG. 8. Case v. Postoperative study demonstrates a successful bypass prosthesis. One year follow-up shows excellent results.

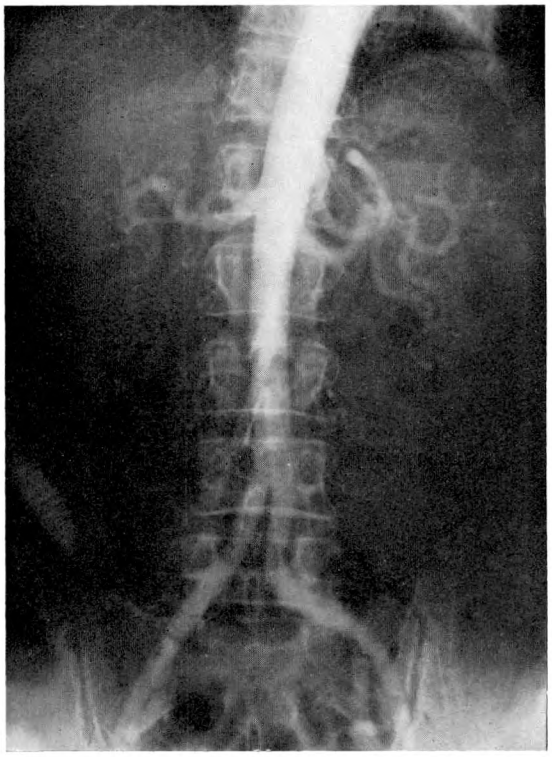


FIG. 10. Case VII. Fifty year old female with hypertension. Intravenous aortogram is considered to be normal.

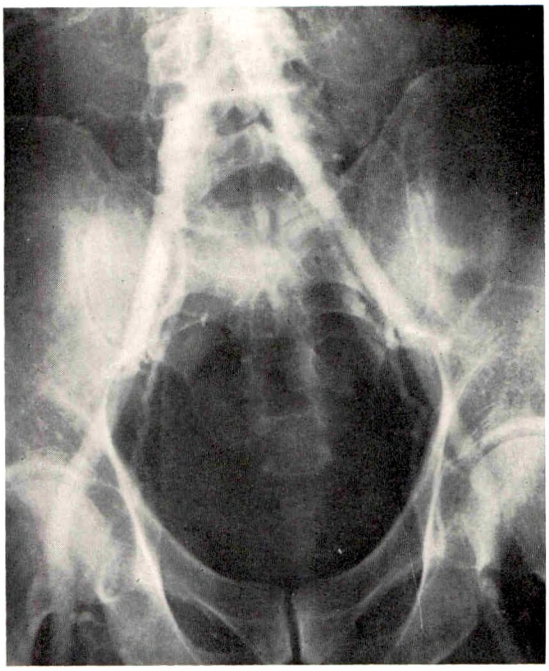


Fig. 11. Case VIII. Sixty-three year old male with intermittent claudication. Initial injection study shows the distal aorta and iliac arteries, therefore ruling out major proximal obstruction.

femoral retrograde aortography, antegrade aortography utilizing cut down techniques with passage of a catheter under fluoroscopic control into the subclavian vein or into the right auricle, and percutaneous intravenous aortography as originally reported by Steinberg using bilateral injection.

We prefer the above described version of percutaneous intravenous aortography because the results have been uniformly good, the complications insignificant, and above all because the technique requires a minimum of equipment and considerably less personnel and time. We believe that the single arm technique produces results comparable to the two arm method and therefore is ideal for the Community Hospital radiologist. A single radiologist usually spends 15 to 30 minutes (intermittently) in performing this examination.

The technique has been successfully employed in 60 cases. The study of the renal vessels has produced results more satisfying

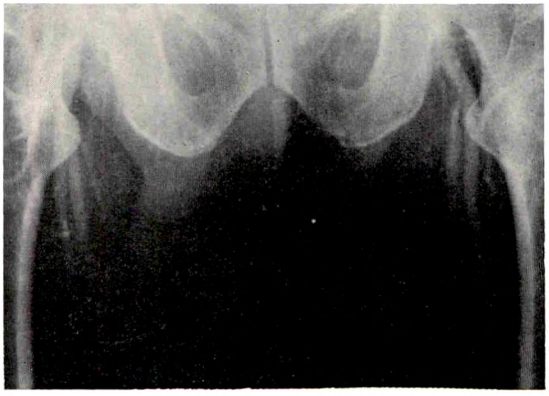


Fig. 12. Case VIII. Second injection study, after lower positioning of the cassette changer, shows normal deep and superficial femoral arteries on the right. On the left the vessels visualized are the deep femoral artery and its branches with no filling of the superficial femoral artery.

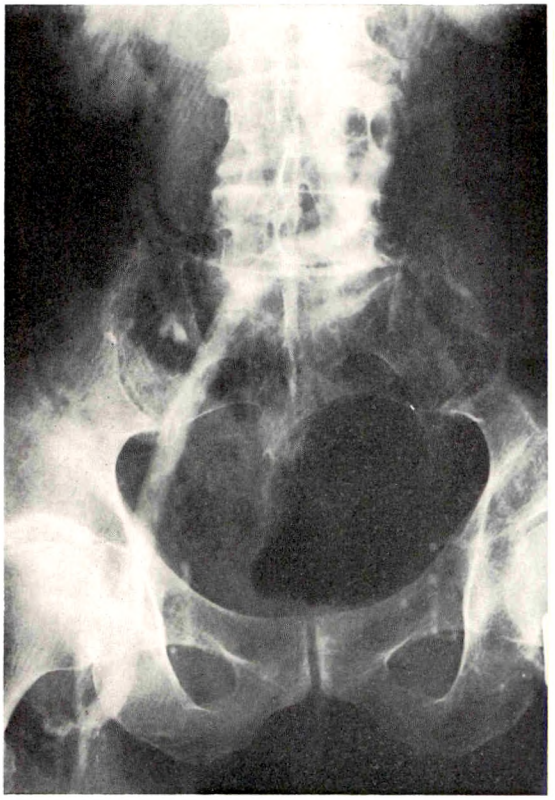


Fig. 13. Case IX. Sixty-six year old male with intermittent claudication. Postoperative study showing a bypass graft connecting the distal aorta and deep femoral artery on the right.

than expected. More recent extension of the technique to the study of the femoral and popliteal vessels has proved equally satisfactory and promises to be perhaps the major application of intravenous methods for arterial study.

SUMMARY

A single arm, large bolus, percutaneous intravenous aortography technique is presented. Hypaque-M, 90 per cent, which has produced maximum opacification with optimum safety in our hands, was used almost exclusively during this study. Successful demonstration of a wide variety of lesions in the aorta and its major branches has been accomplished in a routine manner in 60 cases, covering a period of 18 months. The authors recommend this technique for its uniformly good results and practical adaptability to even the smallest department of radiology.

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THE AXILLARY ARTERY APPROACH TO ARTERIOGRAPHY OF THE AORTA AND ITS BRANCHES*

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ANGIOGRAPHIC diagnosis of various vascular system disorders has become increasingly important with the rapid advances in reconstructive vascular surgical techniques. Accurate diagnosis of arterial lesions, particularly of extracerebral vascular occlusive disease, is not feasible by clinical examination alone, but depends on angiography.[5]

Many methods have been proposed whereby the aorta and its branches can be demonstrated roentgenographically.[6,16] The axillary artery, which offers an excellent route to the aorta, has been almost totally disregarded.[11] In this report our preliminary experiences with this approach will be discussed.

Arterial catheterization is the method of choice for demonstrating a specific vascular bed. For optimum results, the artery selected for puncture should meet the following requirements:

1. Its caliber should be large enough to permit easy introduction of a catheter without risk of spasm.

2. The puncture site should be close to the area under investigation, facilitating maneuverability of the catheter tip into the desired position. Moreover, with a shorter catheter, the speed of injection may be increased.

3. The puncture must be technically simple enough to be consistently successful, and must be of little discomfort to the patient.

4. Complications attributable to catheterization should be minimized, *i.e.:* (a) the vessel should be relatively free of atherosclerotic disease to prevent damage to the diseased vessel or dislodgement of an atheromatous plaque; (b) the area supplied by the vessel should have adequate collateral circulation so that ischemia does not follow local thrombosis that might be caused by catheterization; (c) the technique should not result in such complications as pneumothorax or hemothorax; and (d) the vessel should be available for direct compression to avoid post-puncture bleeding.

The axillary artery meets these requirements. It is a large artery, easily palpated, and can be punctured with little discomfort to the patient. The large vessel allows the introduction of the catheter without spasm. The short distance to the aortic arch makes passage of the catheter into the aorta or the vertebral arteries fairly simple. Direct pressure on the artery after catheter withdrawal has prevented significant post-puncture hematoma. The axillary artery is usually less affected by atherosclerotic disease than is the abdominal aorta or the iliac and femoral arteries. Post-catheterization thrombosis of the axillary artery has not yet been encountered, and the radial pulses have remained easily palpable during and after the procedure. Should the axillary artery be damaged or thrombosed, ischemia is less apt to occur than in similar injury of the femoral or carotid arteries because of the rich collateral supply about the shoulder girdle.

All previously proposed routes of access to the aorta have certain disadvantages which will be reviewed briefly.

The Intravenous Method.[15] With the intravenous method, a total of 90 to 100 cc. of 90 per cent hypaque (1.0–1.2 cc./kg. body wt.) is injected into one or both antecubital veins. A catheter may also be introduced into the femoral or antecubital veins and advanced into the vena cava or right auricle.[13] In our experience with this method, the branches of the aorta, though

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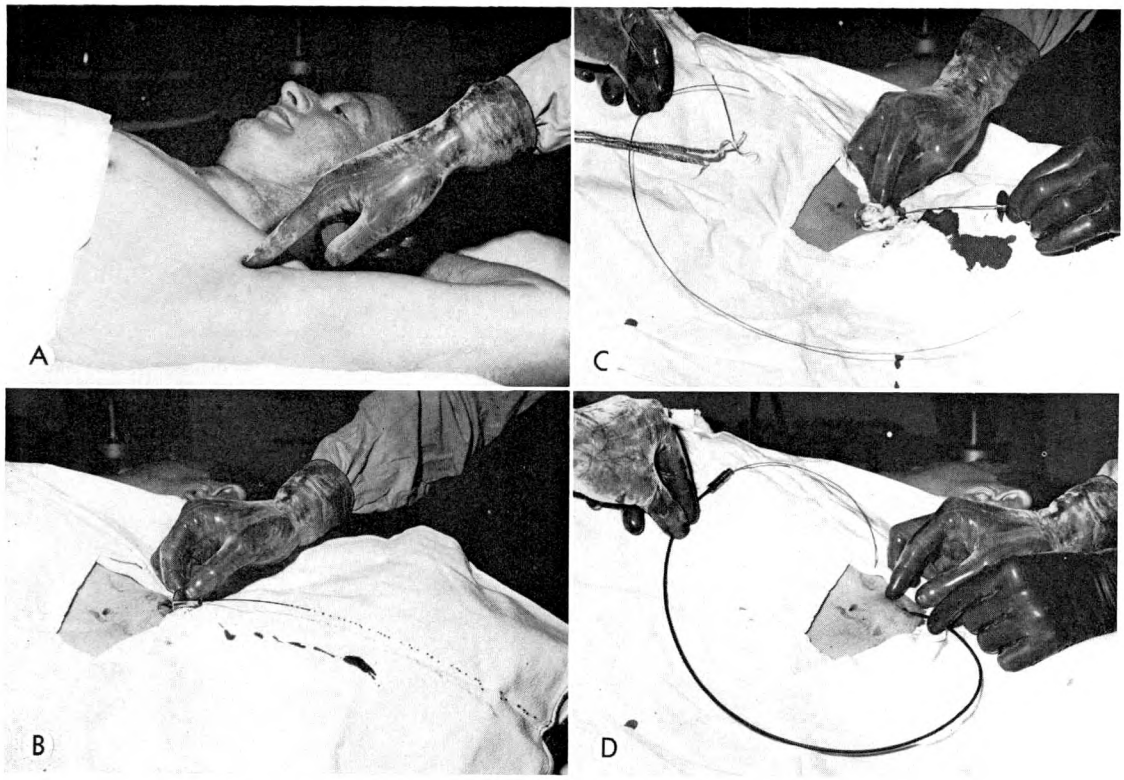


FIG. 1. (*A*, *B*, *C* and *D*) Technique of axillary artery catheterization.

visible, are rarely seen with sufficient clarity to permit necessary evaluation of the degree and extent of an obstructive lesion. In addition, since the injection of contrast medium is at a point distant from the vessels under investigation, a much larger bolus of contrast material must be injected. This approach may, however, be useful in the few patients in whom the arterial catheter cannot be advanced into the desired position because of arterial tortuosity or arteriosclerosis.

Direct Intraventricular Puncture. Contrast medium has been injected directly into the left ventricle in approximately 65 patients at this hospital. Although the roentgenograms of the aortic arch were usually satisfactory, inadequate demonstration of the brachiocephalic vessels was frequent. The procedure appears to have a significant potential risk, as transient arrhythmias, intramuscular injections, and prolonged hypotension were occasionally encountered.

Brachial Artery.[7,9,10] Direct retrograde injection or catheterization of the brachial artery is often performed to show the subclavian artery and its branches. The smaller caliber of the brachial artery, particularly in women, makes the percutaneous puncture more difficult and increases the risk of spasm. Some authors advocate cutdown with direct exposure and incision into the artery. We believe, however, that cutdown procedures should be avoided when safer and simpler percutaneous techniques are available. Moreover, since the puncture site is farther away from the aortic arch, the tip of the catheter is more difficult to maneuver into the desired position. The radial pulse often disappears or is diminished for some time following brachial catheterization. The risk of subsequent vascular insufficiency appears greater with

the brachial than with the axillary artery approach, where multiple collateral vascular channels are available.

Subclavian Artery.[2,8] Direct puncture or catheterization of the subclavian artery has been proposed by many authors. The occurrence of complicating pneumothorax or hemothorax represents one of the major disadvantages in using this vessel. The subclavicular approach to the subclavian artery, proposed by Amplatz and Harner,[1] will undoubtedly decrease the incidence of this complication. However, the vessel is not directly compressible after the puncture, so that local bleeding may be difficult to prevent.

Femoral Artery.[3] The femoral artery offers a useful approach to the abdominal as well as the thoracic aorta. In older patients, atherosclerosis in the abdominal aorta and its branches may be marked. Passage of the catheter into the arch of the aorta via the femoral approach, therefore, may be difficult. It may even be dangerous because of the possibility of perforation, subintimal injection, and dislodgement of an atheromatous plaque.

Carotid Artery.[4] Retrograde injection or

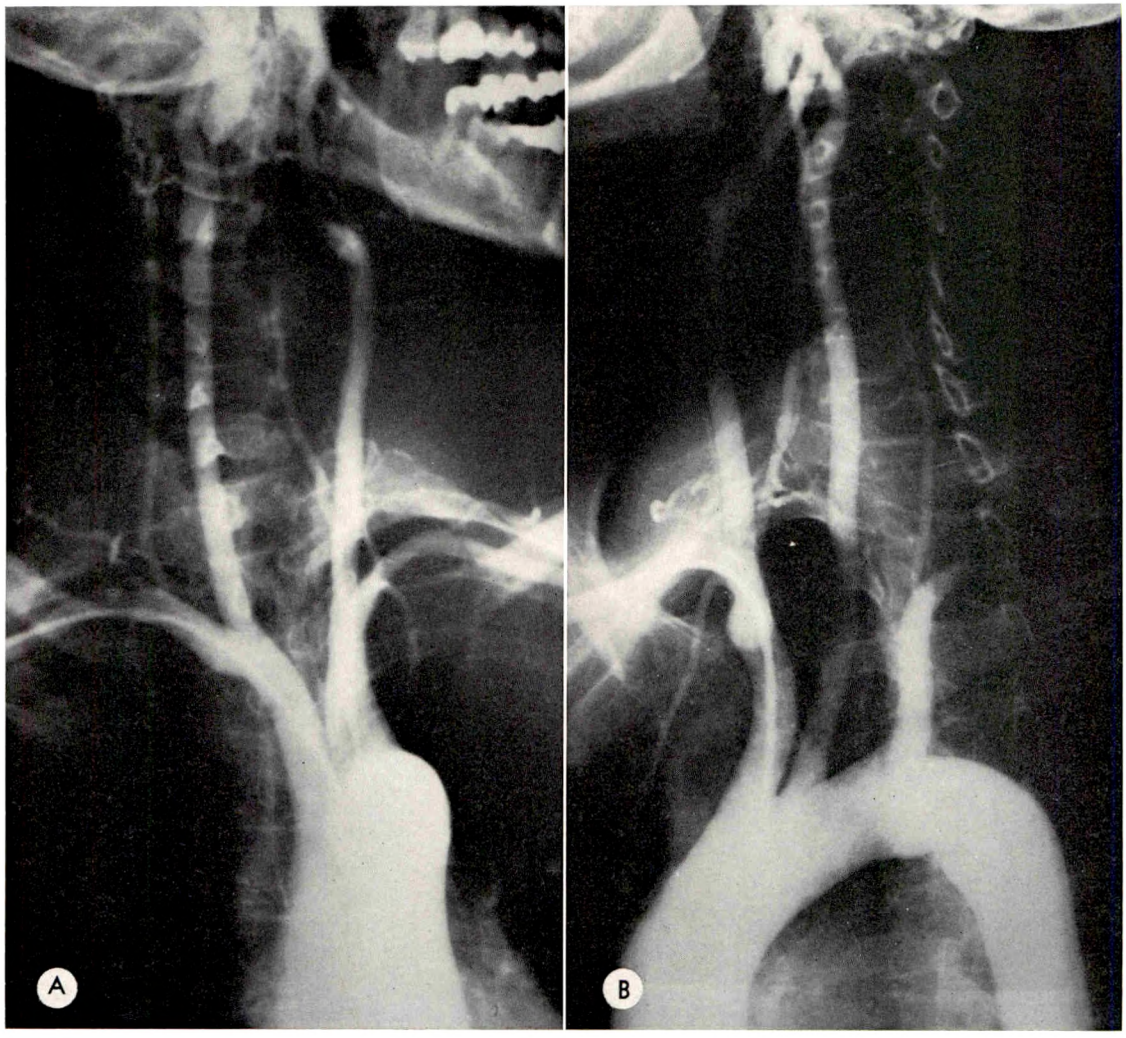


Fig. 2. (*A* and *B*) Normal aortic arch and brachiocephalic arteries.

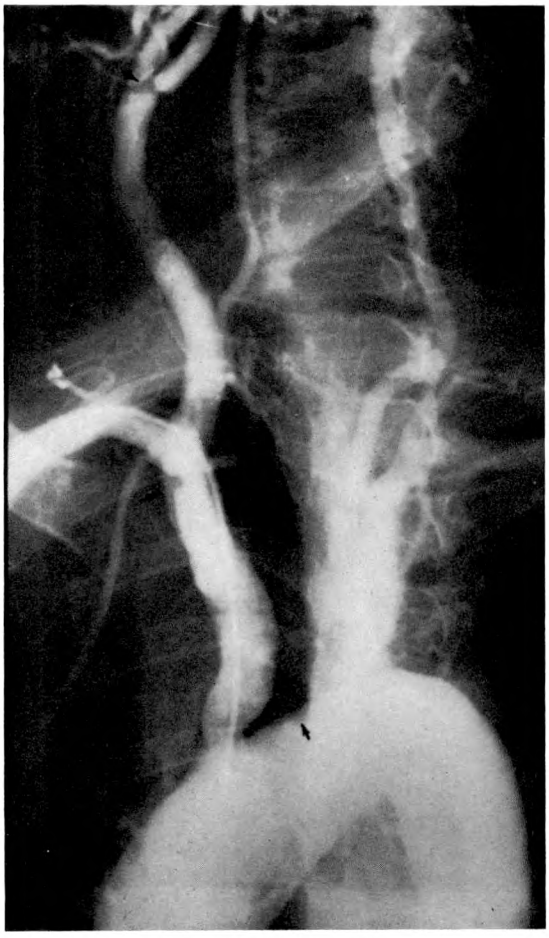


Fig. 3. Complete occlusion of left common carotid artery. Stenosis of right internal carotid and right subclavian arteries.

catheterization of the carotid artery has been proposed to visualize the origin of the common carotid artery or the aortic arch. This technique is not advocated, because of the possibility of damaging those vessels most apt to show atherosclerotic disease. Central nervous system damage may follow such procedures if thrombosis or dislodgement of atheromatous material occurs. Damage to the artery and surrounding tissues also increases the difficulties of reconstructive vascular surgery. Retrograde injection of the vertebral artery, as proposed by Schechter,[12] is not used to examine the origins of the vertebral arteries for similar reasons.

METHOD AND RESULTS

TECHNIQUE OF AXILLARY AORTOGRAPHY

No food or liquids are given in the 4 hours prior to the procedure. Thirty minutes prior to study, the patient receives 50 mg. of benadryl and 50 to 100 mg. of seconal. The patient is placed on the examining table in the supine position with the appropriate arm raised over his head (Fig. 1*A*). The axillary artery is palpated high in the axilla and local anesthesia is achieved at the puncture site. A 5 mm. incision is made into the skin to facilitate

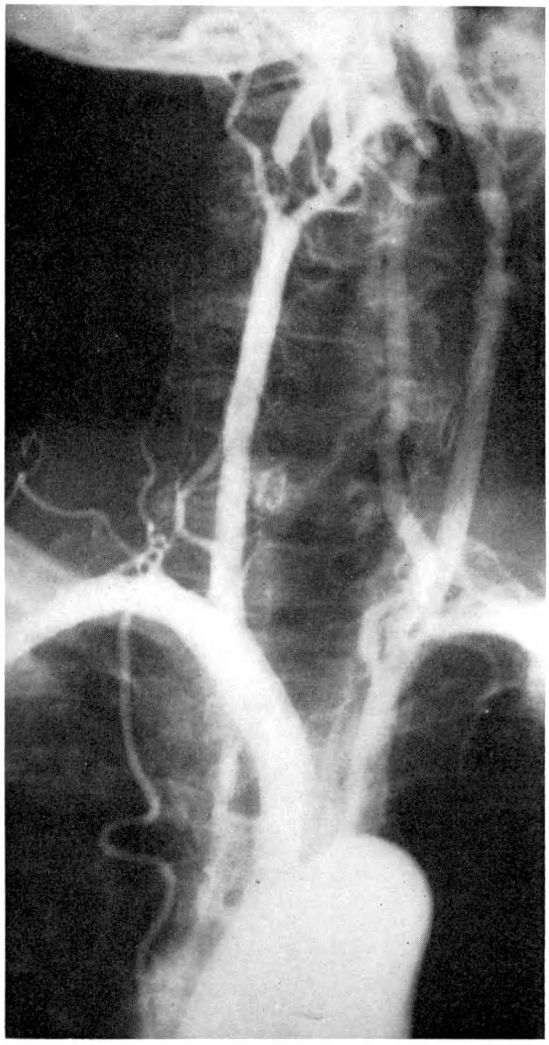


Fig. 4. Marked stenosis of right internal carotid artery. Slight stenosis of left internal carotid artery.

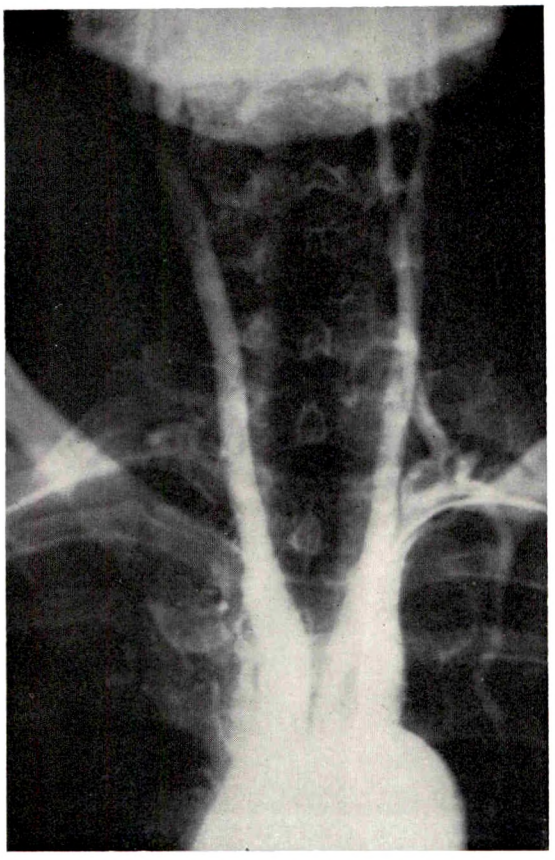


Fig. 5. Occlusion of right subclavian artery.

later passage of the catheter. The Seldinger technique of arterial catheterization is used.[14] The artery is punctured with a thin-walled, 18 gauge needle (Fig. 1*B*), after which a stainless steel, coiled spring guide wire (outside diameter of .036 inches) is inserted and the needle withdrawn (Fig. 1*C*). A catheter with a tapered tip is inserted into the artery over the guide wire which is then withdrawn (Fig. 1*D*). In our experience, the placement of the guide wire and catheter has been controlled fluoroscopically. To avoid the necessity for dark adaptation, image amplification or television fluoroscopy is helpful. For aortic arch or abdominal aortic studies, a No. 7 or No. 8 French, thin walled, teflon catheter* is used. To avoid recoil, to increase injection speed, and to produce a bolus which fills the artery uniformly, four to five side holes are placed adjacent to the tip of the catheter. During the procedure, the catheter is often flushed with 2.5 per cent sodium citrate in normal saline to prevent clotting. A pressure injector is used to deliver the contrast medium to the aorta rapidly. For aortic arch studies, blood pressure cuffs, placed on both arms, are inflated to above systolic blood pressure during the injection. At the end of the procedure, the catheter is withdrawn, and direct pressure on the artery is maintained for at least 10 minutes.

* U. S. Catheter and Instrument Corporation, Glens Falls, New York.

USES OF THE AXILLARY ARTERY APPROACH

We have found the axillary artery approach most useful in surveying patients with suspected extracranial arterial disease. In these patients, the right axillary artery is usually chosen as the site of puncture for catheterization. The distal part of

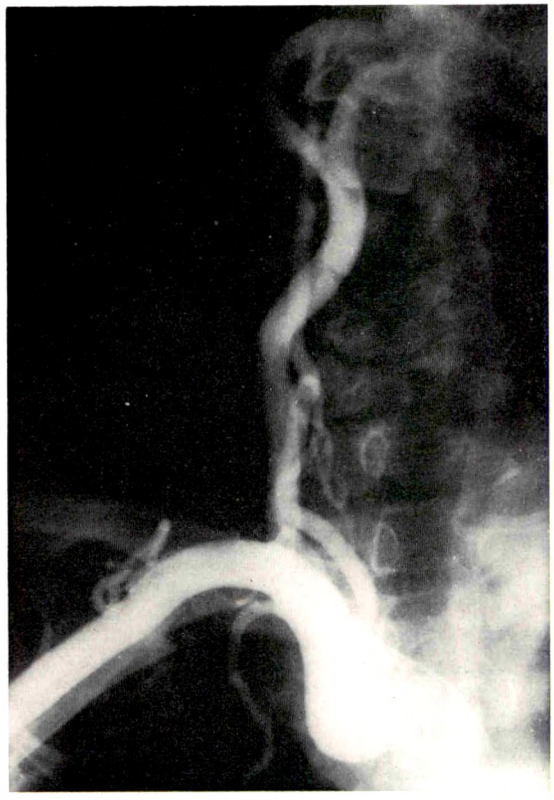


Fig. 6. Tortuous innominate and right carotid arteries.

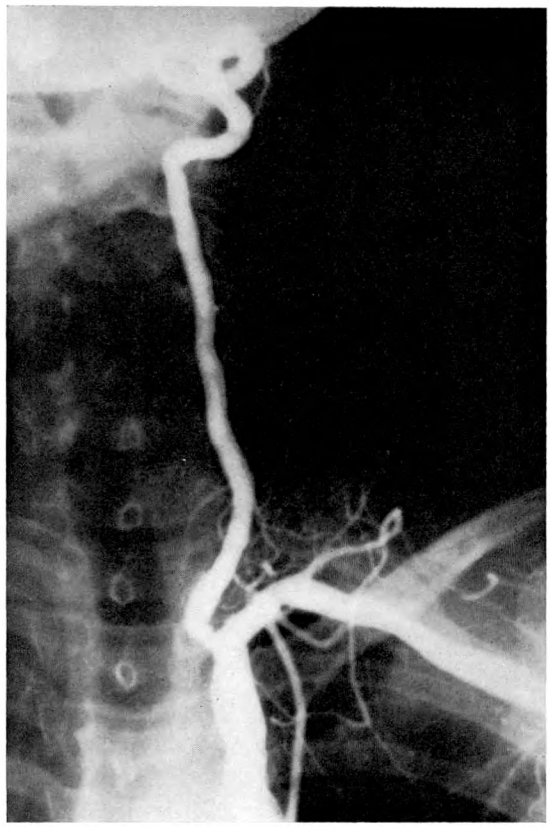


Fig. 7. Slight narrowing of origin of left vertebral artery.

the catheter is slightly precurved and its tip advanced to the ascending aorta to a level approximately 5 cm. distal to the aortic valves. In patients with tortuous subclavian and innominate arteries, it may be difficult to maneuver the catheter into the aortic arch. It is, therefore, important to have catheters available with varying curvatures. Usually, two injections, each of 40 cc. of 76 per cent renografin, are made. One injection is made with the patient in the anteroposterior position with his head turned to the left (Fig. 2*A*); the other is made with the patient in the right posterior oblique position and his head turned to the right (Fig. 2*B*). Thus, the entire extracranial arterial tree is outlined with one puncture (Fig. 3, 4 and 5). However, it is important to study the intracranial circulation also to eliminate the possibility of intracranial pathology. The catheter may be withdrawn into either the innominate or the subclavian artery so that the right carotid and vertebrobasilar systems are better seen (Fig. 6 and 7). In this case, only 15 to 20 cc. of contrast material is injected. For patients undergoing the advisable, complete, four vessel study for cerebrovascular occlusive disease, adequate visualization of the left carotid and vertebral arteries is not always obtained. On these occasions, later injections of the left common carotid and left axillary arteries are performed. Simultaneous anteroposterior roentgenograms of the aortic arch and neck with lateral roentgenograms of the neck and intracranial circulation would be useful; the biplane equipment for obtaining these has not been available to us. The axillary approach is very useful, also, for evaluation of postoperative results without danger of damaging the recently repaired vessel.

The vertebral artery may be catheterized directly, using the axillary artery approach. In this case, a catheter of smaller caliber with end hole only is recommended. The right vertebral artery is more easily catheterized than the left because of the difference in anatomic relationships on the two sides. If vertebral artery catheterization is unsuccessful, injection into the subclavian artery usually produces good results.

The axillary artery approach would also seem to be ideal for coronary angiography, although we have had no occasion to use it for this procedure.

Most studies of the abdominal aorta are performed via the femoral route; however, on occasion, we have used the axillary artery approach to examine the descending thoracic or abdominal aorta. The catheter is usually more easily maneuvered into the descending aorta from the left axillary artery, rather than the right, by using a slightly curved catheter. The axillary artery approach has been particularly useful in patients with coarctation of the aorta, aortic aneurysms, or very marked atherosclerosis of the aortic, femoral, or iliac

vessels (Fig. 8, *A* and *B*, 9 and 10). In these patients, the upward passage of the catheter may be difficult and dangerous. We have also used this approach to examine the renal arteries, particularly following thromboendarterectomy (Fig. 11). The possibility of damage to the postoperative aorta and renal arteries is minimized by approaching this area from above and placing the tip of the catheter above the site of operation.

COMPLICATIONS

In our series of 160 axillary aortographies, no serious local complications have been noted. As a rule, the artery is easily punctured. There are occasions when branches of the brachial plexus are entered, causing temporary pain down the elbow and into the hand. No permanent nerve damage has been encountered, nor has post-puncture hematoma been a serious problem. The radial pulses have been easily palpable during and after the procedure in most cases. In 5 patients, a transient loss of the radial pulse was encountered.

The only complications of note were those due to technical errors. In one patient, a transient hemiparesis developed following the inadvertent injection of 40 cc. of contrast medium directly into the innominate artery. In another patient with marked arterial tortuosity, attempts to maneuver the catheter into the arch of the aorta were unsuccessful. A test injection of contrast material, with the tip of

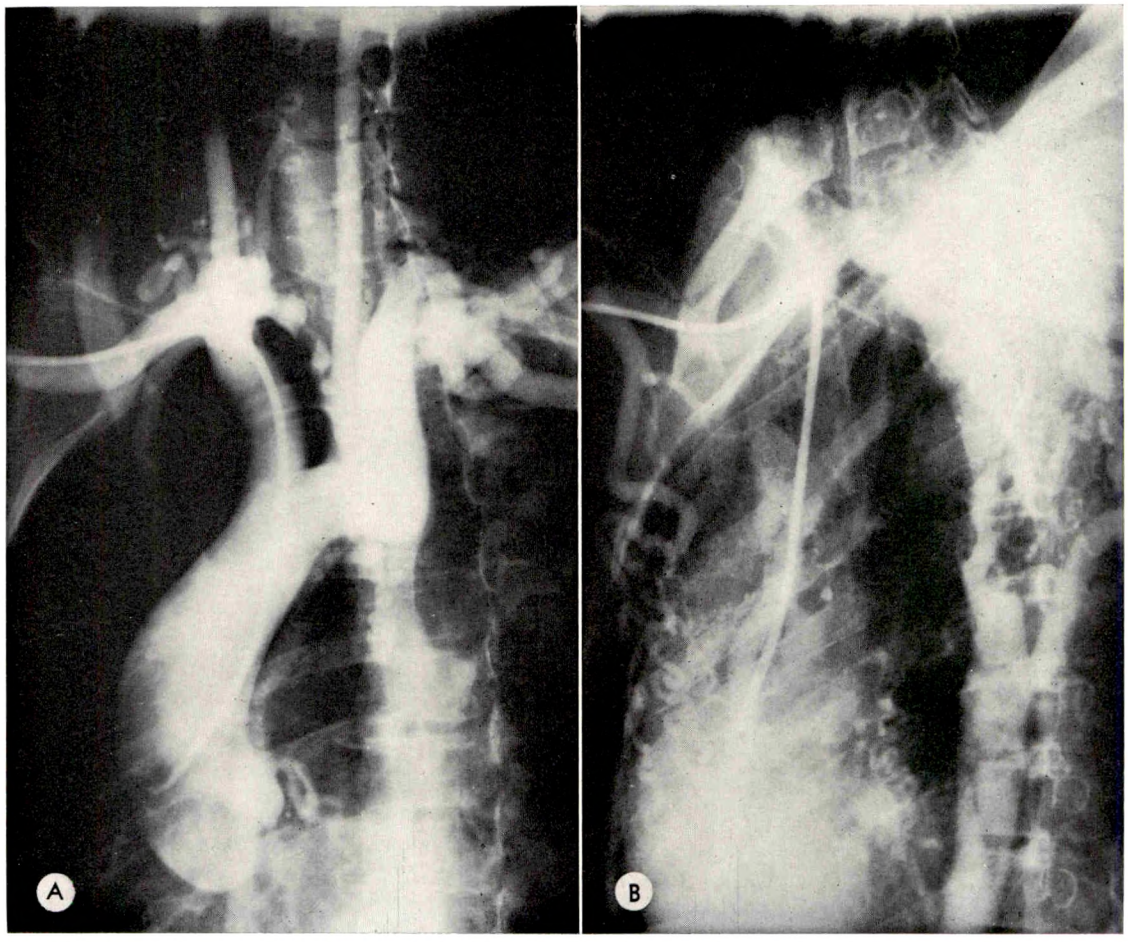


Fig. 8. (*A* and *B*) Coarctation of aorta with extensive collateral circulation.

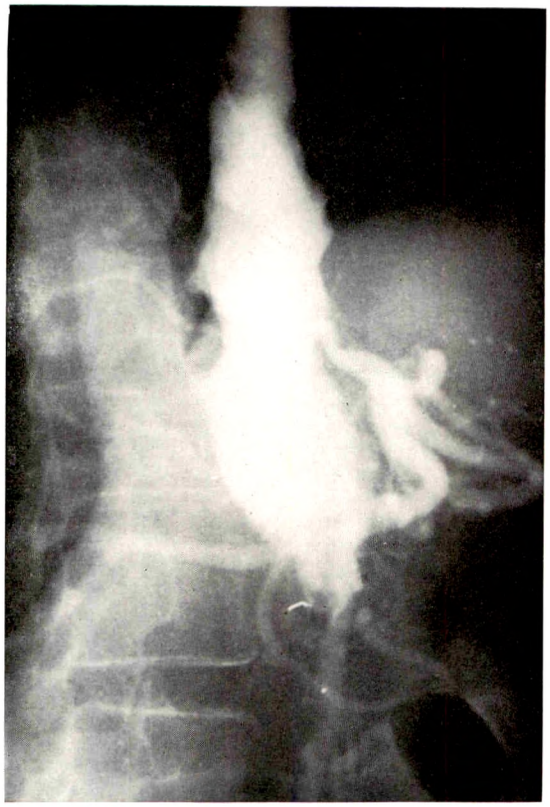
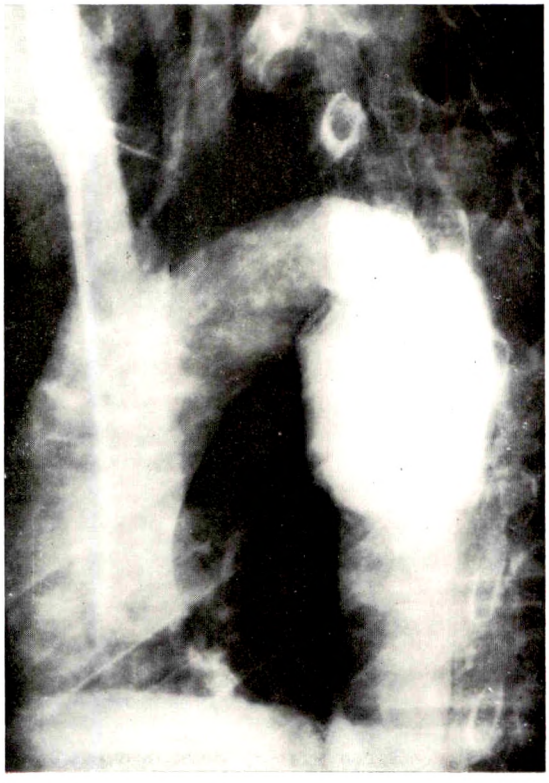


Fig. 9. Marked atherosclerosis of abdominal aorta with stenosis at origin of celiac axis.

the catheter in the subclavian artery, disclosed a partial extravascular injection. The patient noted transient pain in the shoulder, but had no other sequelae. Similar partial extravasations were noted in 3 other patients with the test injection of 5 cc. of contrast material. This complication can be avoided by having catheters with differing curves available and by advancing the relatively stiff catheter only after the flexible wire guide has been adequately positioned fluoroscopically.



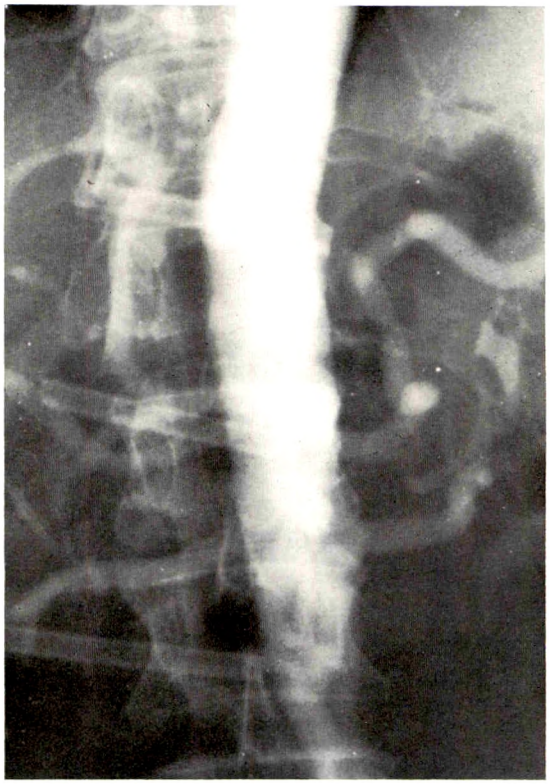


Fig. 11. Postoperative renal thromboendarterectomy.

Fig. 10. Traumatic aneurysm of aorta.

CONCLUSION

Arteriograms, using the axillary artery approach, have been obtained in 160 instances. The axillary artery is a large vessel, relatively free of atherosclerotic disease. It can easily be punctured percutaneously, and post-catheterization hematoma can be avoided by direct compression. This artery, therefore, offers a simple, safe approach to the ascending and descending portions of the aorta and its branches. It has proved to be particularly useful in evaluating patients with suspected extracranial arterial disease, since all the brachiocephalic vessels can be demonstrated using one arterial puncture. This method may also be used to study the descending aorta, renal, or femoral arteries, where the transfemoral route is not indicated. In our series, no serious complications have occurred. The transaxillary approach to the aorta appears to be superior to many other routes previously utilized.

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INTRAVENOUS ABDOMINAL AORTOTOMOGRAPHY*

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TOMOGRAPHY (body-section roentgenography, planigraphy) of the intravenously opacified abdominal aorta began in this center in 1954 when Evans and his associates[5] commenced their studies in nephrotomography. With a single rapid intravenous injection of concentrated organic iodide medium, the abdominal aorta, especially in thin individuals, was visualized in 40 to 50 per cent of the cases. In 1959, with the advent of the method of simultaneous, rapid, bilateral intravenous injections of contrast agents, dosages of 1 ml. per kg. of body weight could be given as a bolus, and as a result the abdominal aorta was opacified in practically every instance.[11,12] Following this, Liese[8] in 1960 published a preliminary report of abdominal aortic body-section roentgenography which he termed, angiotomography. However, it would appear that aortotomography is the better way to describe the procedure, especially because nephrotomography has become widely accepted as the designation for the technique of tomography of the nephrographic phase of the kidneys.[3,4,6,9]

This report deals with the technique of intravenous abdominal aortotomography and its value in diagnosis of arteriosclerotic occlusive and aneurysmal disease of the abdominal aorta.

METHOD AND MATERIALS

Tomography of the intravenously opacified aorta is secured by positioning the patient in the supine position on a table which contains a book-cassette capable of being simultaneously exposed. The latter is a commercially available apparatus (Halsey) and consists of 7 specially matched, 1 cm. apart, 14 by 14 inch screens. The roentgen apparatus is of conventional commercial design. The technical factors are 70 ma., 40 inch target film distance at an exposure of 6 seconds and 70 kvp. for 20 cm. abdominal thickness. A preliminary tomographic cut serves as a guide for technique; the 7 tomographic roentgenograms (cuts) are made simultaneously usually at distances of 11 to 17 cm. (1 cm. apart) from the table top.

The method of intravenous aortography described in 1959[11] is used for opacification of the abdominal aorta. Recently, the use of an automatic table has permitted serial roentgenography of the abdominal aorta and peripheral vascular systems.[16] Timing of the exposure of the abdominal aorta, however, still depends upon determination of the decholin circulation time.[11] Because aortotomography is usually performed after a complete survey of the abdominal aortic and peripheral vascular system, the 6 second exposure time of the simultaneous book-cassette can be estimated after viewing the abdominal aortographic series. For example, since the average decholin circulation time is often 10 seconds, the following program can be planned. The Schönander film magazine is loaded with 14 films arranged in a predetermined series with blank slots between each series to allow for movement of the table. Usually, 5 films at 0.75 second intervals are made of the abdomen and 3 exposures each of the pelvis, thighs and legs respectively.[16] After viewing the degree of opacification of the abdominal aorta, the 6 second interval which will provide maximal opacification during tomography can readily be estimated. In practice, in the average patient with decholin circulation of 10 seconds, exposure of the aortotomogram usually begins at 9 seconds and ends at 15 seconds.

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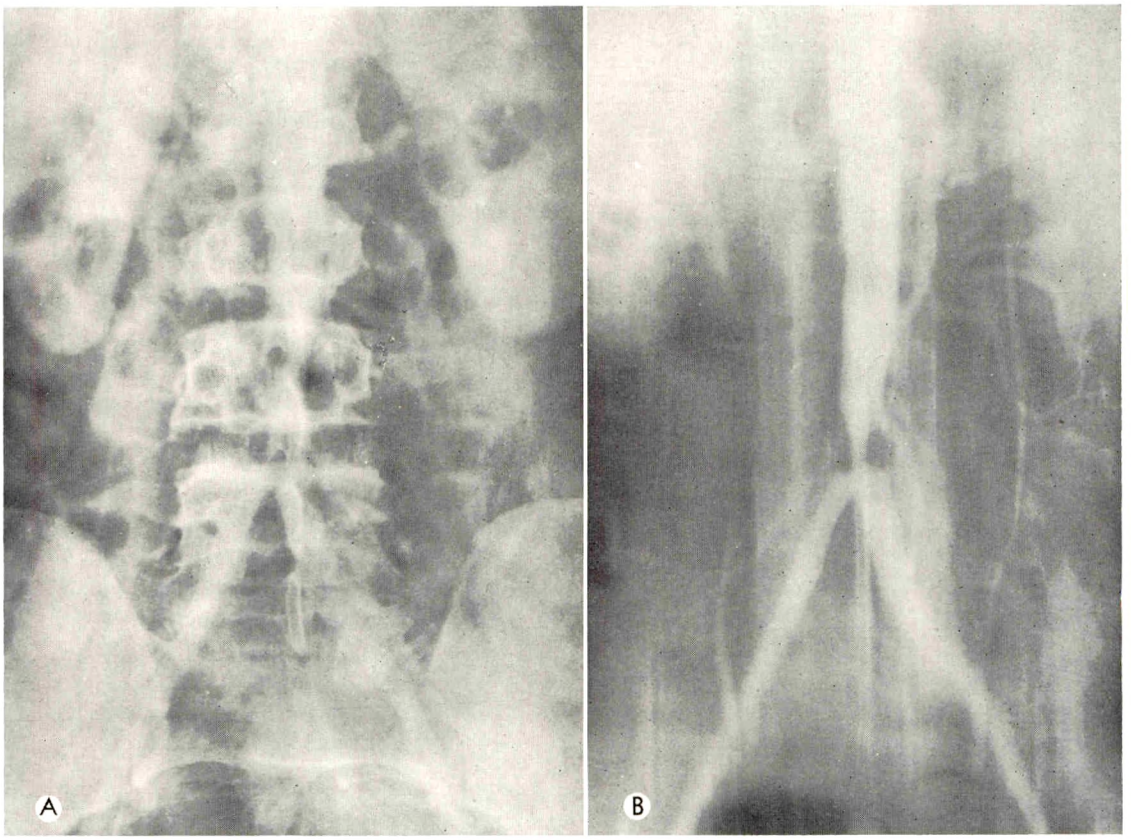


Fig. 1. Arteriosclerotic occlusive disease of the abdominal aorta involving the origins of the common iliac arteries in a 41 year old man, with bilateral intermittent claudication of the buttocks. (*A*) Serial intravenous abdominal aortogram showing narrowing and irregularity of the lower portion of the abdominal aorta especially at the bifurcation. (*B*) Aortotomogram, selected from a series of 7 cuts, readily reveals the irregularly deformed abdominal aorta which almost becomes occluded at the bifurcation. Note visualization of the superior mesenteric and colonic arterial system.

Following the series, a routine pyelogram (with the Potter-Bucky grid) is made.

To date, 41 patients have had aortotomography. This is less than 10 per cent of the 435 patients that have had abdominal aortography with the intravenous method of simultaneous bilateral injection of concentrated contrast media.[14] Thirty-two were males and 9 were females. The ages ranged from 39 to 75 years; the average was 58.2 years. Thirteen patients in this group were hypertensive at the time of study (over 150/90 mm. Hg). Twenty-three patients had occlusive disease of the abdominal aorta or aortoiliac arterial branches, 8 had arteriosclerosis (tortuosity but without calcific deposits) of the abdominal aorta and aortoiliac system, 6 had abdominal aortic aneurysms, and 4 had both occlusive and aneurysmal disease of the abdominal aorta.

RESULTS

Figure 1, *A* and *B* is an example of the value of intravenous aortotomography in occlusive disease of the abdominal aorta. The serial intravenous abdominal aortogram (Fig. 1*A*) shows narrowing of the abdominal aorta several centimeters beyond intact renal arteries. This is especially marked above the bifurcation of the abdominal aorta. The right common iliac artery seems smaller than the left. Intravenous aortotomography (Fig. 1*B*) clearly

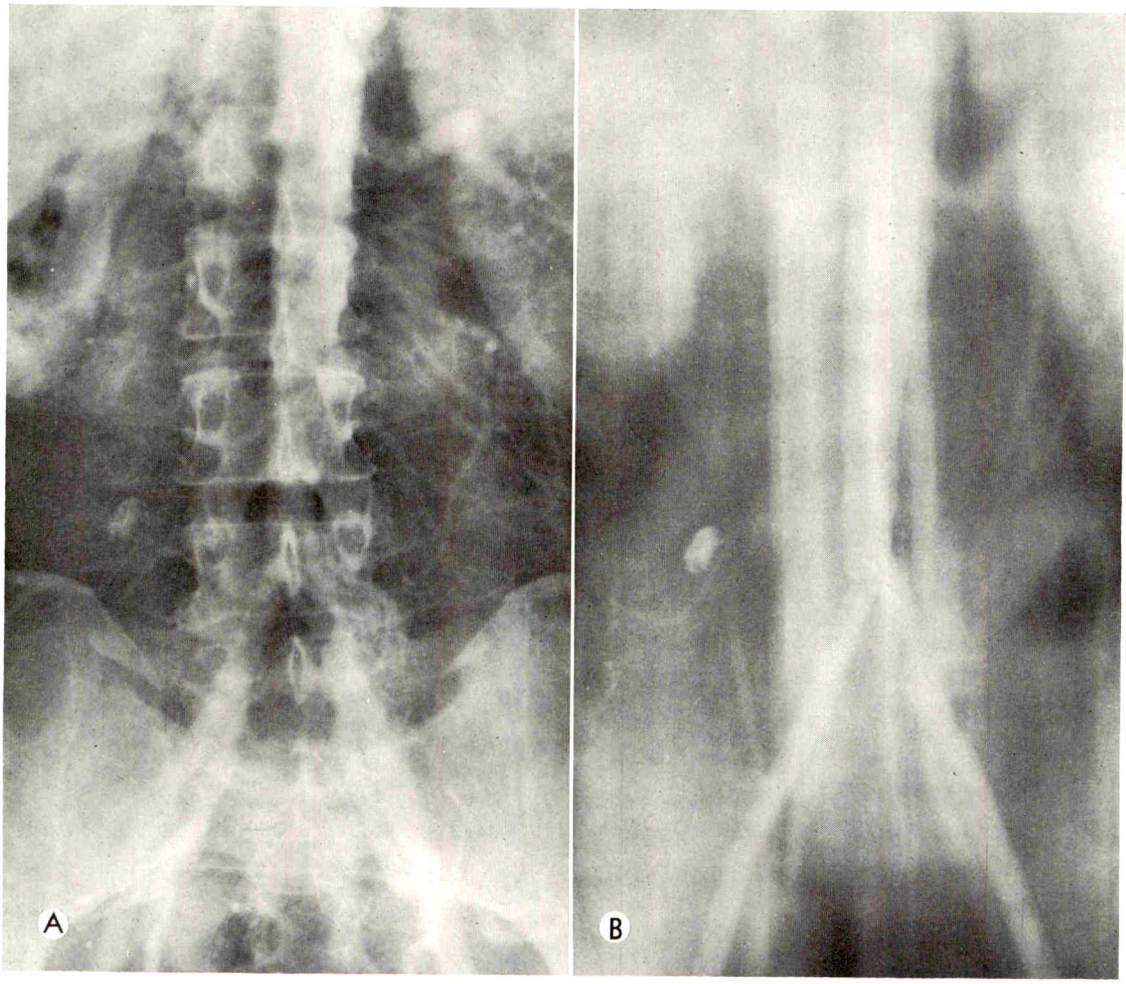


FIG. 2. Severe intermittent claudication of both legs of 1 year's duration in a 40 year old man. (*A*) Intravenous abdominal aortogram discloses marked irregularity and narrowing of the lower half of the abdominal aorta. At the origin of the left common iliac artery, there is partial occlusion of the vessel with poststenotic dilatation distally. The origin of the right common iliac artery is also narrowed and irregular. (*B*) Aortotomogram readily reveals the severe abdominal aortic narrowing, especially at the bifurcation where the origins of both common iliac arteries are partially occluded.

reveals the narrowing of the abdominal aorta by occlusive disease several centimeters above the bifurcation, especially along the left wall of the aorta. Constriction of the aorta at the bifurcation by thrombus is evident. The left common iliac artery seems poststenotically dilated, whereas the right common iliac artery is somewhat hypoplastic. Figure 2, *A* and *B* is another illustration of how aortotomography precisely and accurately localized occlusive disease involving the aortoiliac system. The intravenous serial aortogram (Fig. 2*A*) shows narrowing of the abdominal aorta well below intact renal arteries. Tapering of the abdominal aorta is especially noticeable at the bifurcation of the abdominal aorta. Both common iliac arteries are reduced in caliber, the left rather abruptly. The aortotomogram (Fig. 2*B*) clearly reveals the irregularity of the abdominal aorta owing to thrombus along the left outer wall, especially at the aortic bifurcation. More important, though, are the clear-cut deformities just beyond the origins of the common iliac arteries, especially the left.

The hypoplastic right common iliac artery and the poststenotically dilated left common iliac artery are apparently secondary to occlusive disease in the vicinity of the aortic bifurcation. Figure 3 is still another example of severe abdominal aortic occlusive disease involving the lower half and bifurcation of the aorta. In this patient, a bypass operation a year earlier for occlusive disease of the right superficial femoral artery had failed to relieve severe intermittent claudication. Occlusive disease of the abdominal aorta with complete occlusion of the left common iliac artery is shown in Figure 4, *A* and *B*. In this instance, narrowing of the abdominal aorta began just below the origins of intact renal arteries (Fig. 4*A*). The left common iliac artery was not visualized, the right common iliac artery was irregular in contour and poorly opacified. The severity of the arteriosclerotic occlusive disease is well demonstrated in Figure 4*B*. Most of the left outer wall of the abdominal aorta is narrowed by thrombus and the right abdominal aortic wall is irregular. The abrupt occlusion of the left common iliac artery at its origin is well shown. The segmental character of the occlusion is recognized by visualization of the distal portion of the left common femoral artery. On the right side, almost complete occlusion of the right common iliac artery with areas of poststenotic dilatation followed by partial occlusion of the common femoral artery is striking. In a patient with a poorly opacified aorta beyond the celiac axis (Fig. 5*A*), marked narrowing and poor opacification of the abdominal aorta was associated with calcific deposits along both outer walls of the abdominal aorta, especially at the bifurcation (Fig. 5*B*).

Aortotomography can enhance visualization of aneurysms of the abdominal aorta. For instance, the serial abdominal aortogram (Fig. 6*A*) fails to clearly visualize blood flow into the common iliac arteries, whereas the aortotomogram (Fig. 6*B*), made at the appropriate level, clearly shows them to be intact. In addition, the linear calcification of a laminated thrombus several centimeters from the left wall of the aneurysm is also clearly revealed. Figure 7, in contrast, shows partial narrowing of the origins of both common iliac arteries in a patient with a large sacciform aneurysm of the abdominal aorta. Here too, the irregular walls of the aneurysm lined by thrombus laterally are revealed. Aortotomography because it reveals the abdominal aorta at various levels, can also help to distinguish overlying structures. For instance, bowel containing gas was superimposed on an abdominal aneurysm in a patient (Fig. 8*A*). The aortotomogram (Fig. 8*B*) made at different levels clearly excluded thrombus in the aneurysm. On the

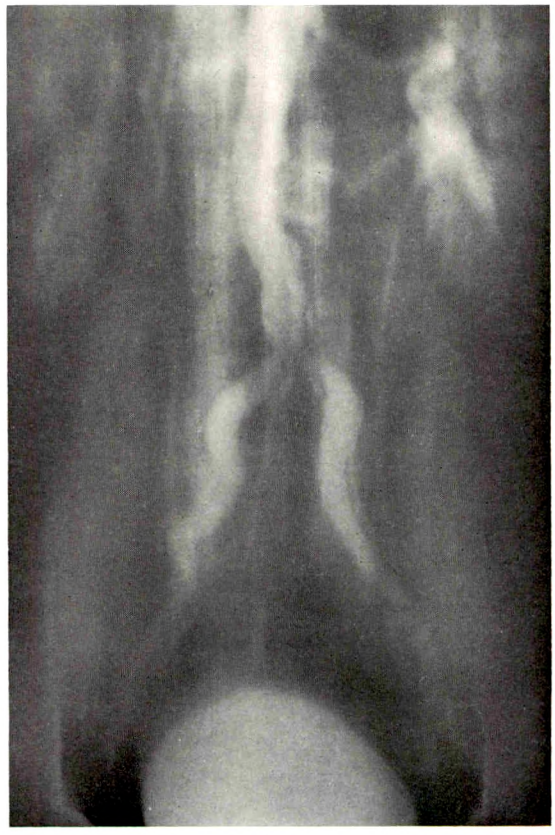


Fig. 3. Intermittent claudication of both calves in a 65 year old man. Aortotomogram discloses marked thrombotic disease and tortuosity of the abdominal aorta and aortoiliac arteries. There is calcification at the aortic bifurcation and both common iliac artery origins are almost completely occluded.

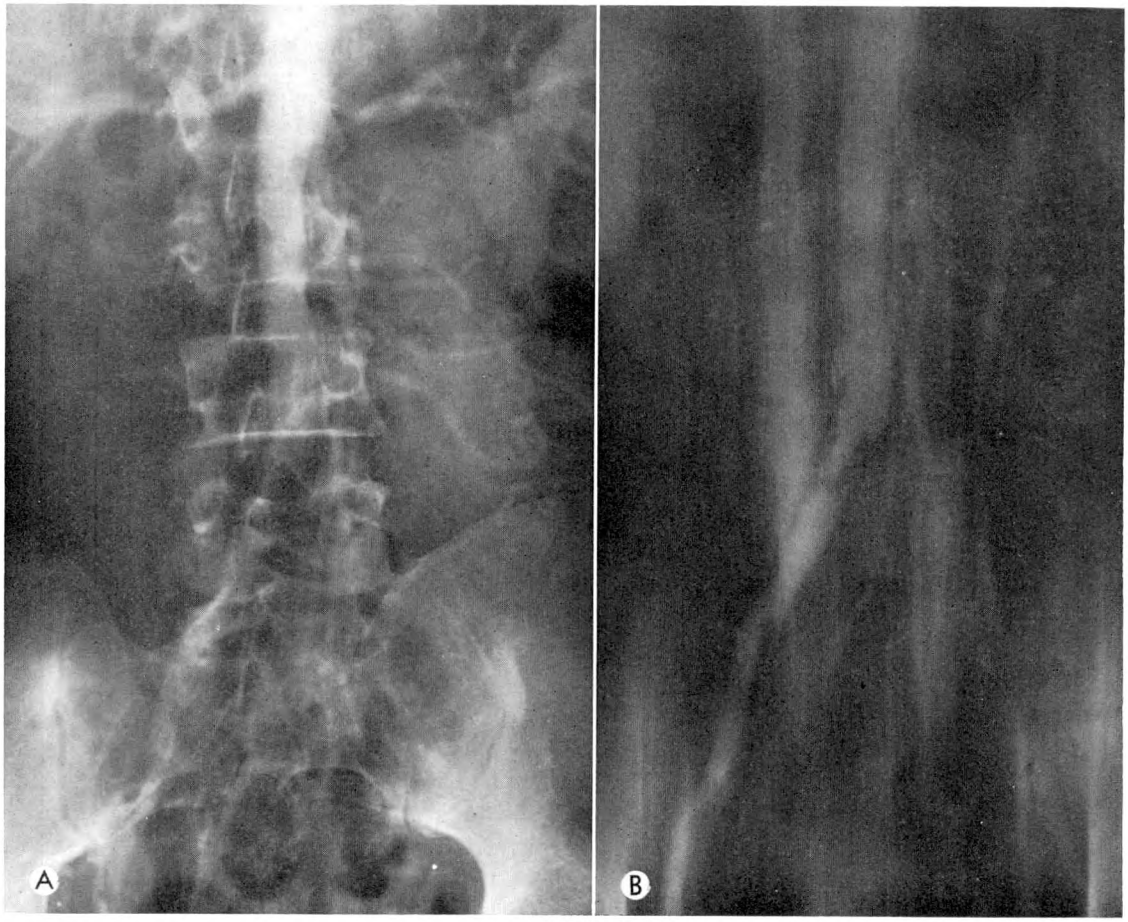


FIG. 4. Intermittent claudication of the legs, left more than the right, of 2 years' duration in a 48 year old man. (*A*) Intravenous aortogram discloses severe narrowing of the left side of the abdominal aorta just below intact renal arteries. The left common iliac artery is completely occluded. The bifurcation of the abdominal aorta is obscure and the right common iliac artery is seen only vaguely. (*B*) Aortotomogram also shows severe arteriosclerotic disease with abrupt occlusion of the left common iliac artery at the aortic bifurcation. Note visualization of the left common femoral arteries by collaterals. The right border of the aortic bifurcation is unusually deformed by arteriosclerotic plaques. The origin of the right common femoral artery is severely constricted, while the remainder of the right aortoiliac artery is markedly irregular and tortuous due to arteriosclerosis.

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FIG. 6. Huge arteriosclerotic abdominal aortic aneurysm in a 68 year old man. (*A*) Intravenous abdominal aortogram showing the aneurysm lined by a large thrombus along its left outer wall. Arrow indicates marked linear calcification of the thrombus. Because of tortuosity, the common iliac arteries were poorly outlined. (*B*) Aortotomogram well demonstrates the aneurysm, left wall calcification (arrow) and thrombus. Note the intact tortuous common iliac arteries.

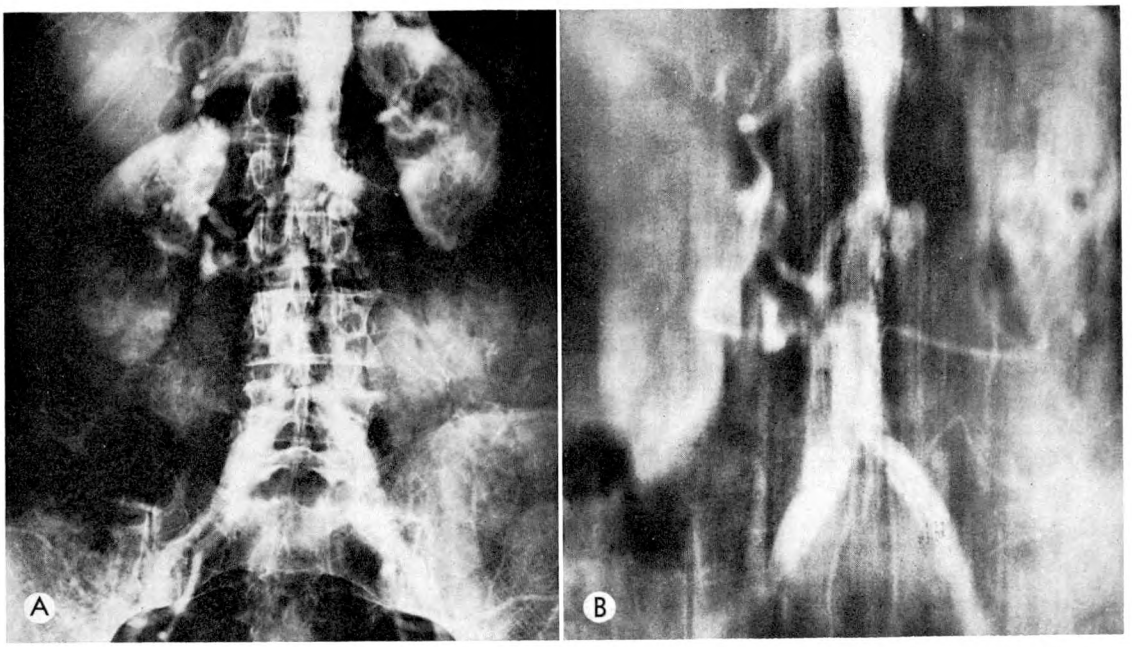
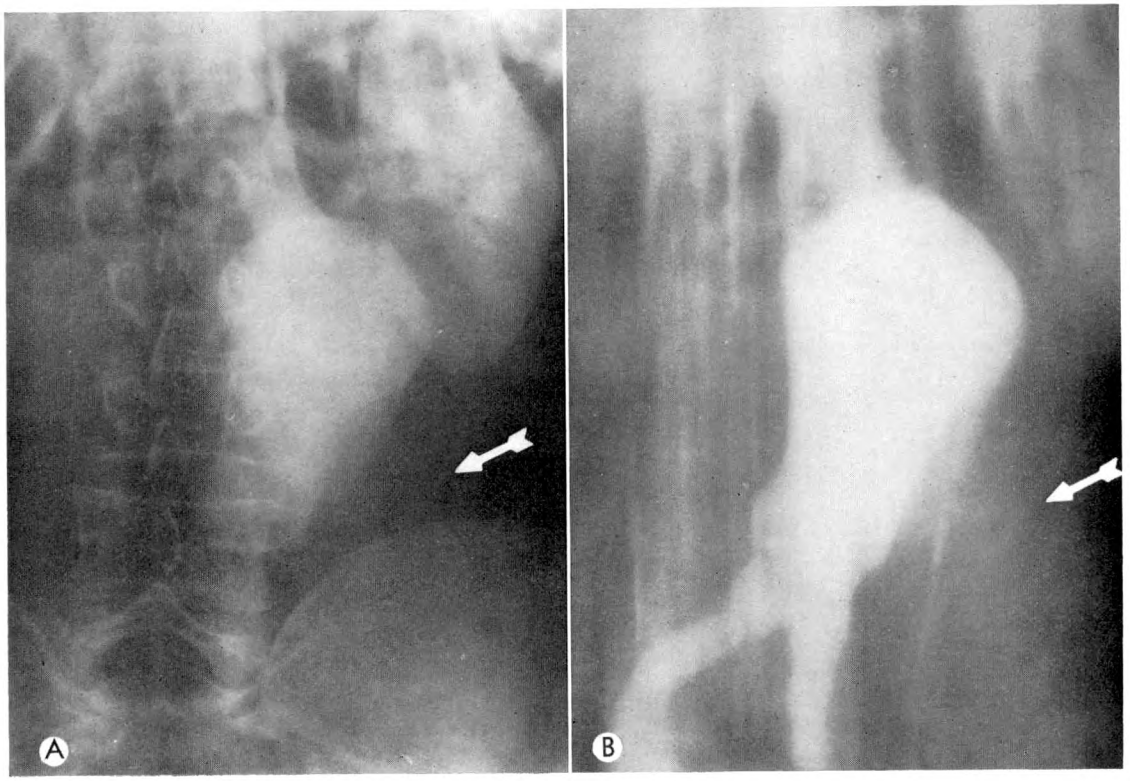


Fig. 5. Low back pain in a 50 year old woman. (*A*) Intravenous abdominal aortogram showing a poorly opacified abdominal aorta with tortuous but intact iliofemoral branches. (*B*) Aortotomogram (logEtronic reproduction) revealing severe occlusive abdominal aortic disease. There are large linear calcifications along the abdominal aorta and bifurcation with partial stenosis of both common iliac arteries at their origins.



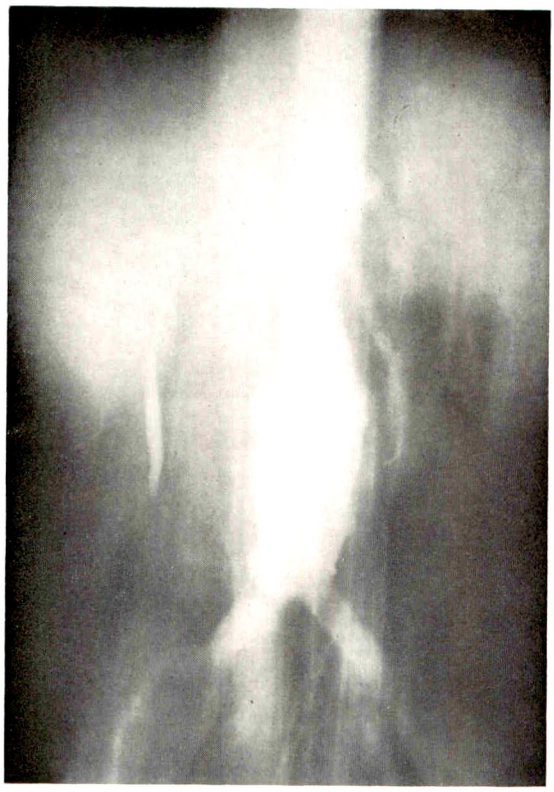


FIG. 9. Aneurysmal and occlusive disease of the abdominal aortic and iliofemoral system in a hypertensive (170/80 mm. Hg) man of 61 years. (*A*) Intravenous abdominal aortogram showing a filling defect of the aorta along the right border opposite the origin of a poorly visualized and stenotic right renal artery. The aorta below the renal arteries is aneurysmal. Partial occlusion of the left common iliac artery at its origin is also evident. (*B*) Aortotomogram emphasizes the aneurysmal and occlusive features of *A*.

FIG. 7. Huge abdominal aortic aneurysm in a 63 year old man well visualized on an intravenous aortotomogram. The constrictions of the common iliac arteries at their origins were verified at operation; resection of the aneurysm beyond the stenotic areas and replacement with a synthetic graft were curative.

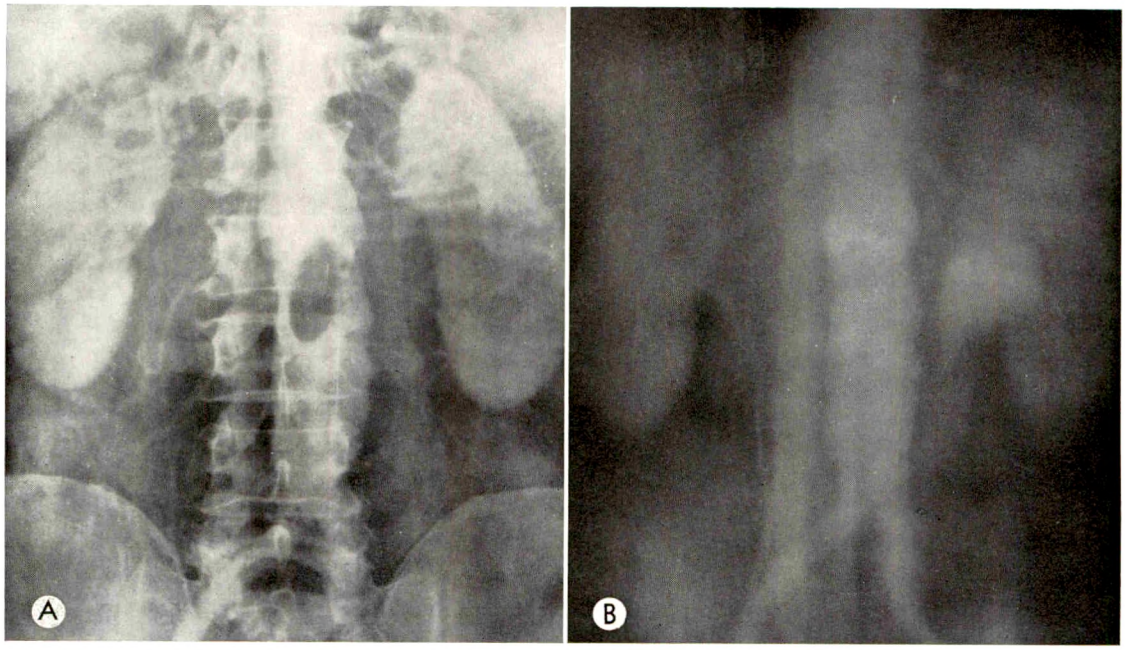


FIG. 8. Large abdominal aortic aneurysm beginning at the renal arteries in a 62 year old man. (*A*) Intravenous abdominal aortogram showing a filling defect that appeared to be within the aortic shadow. (*B*) Aortotomogram, however, showed it to be an extraneous overlying gaseous viscus.

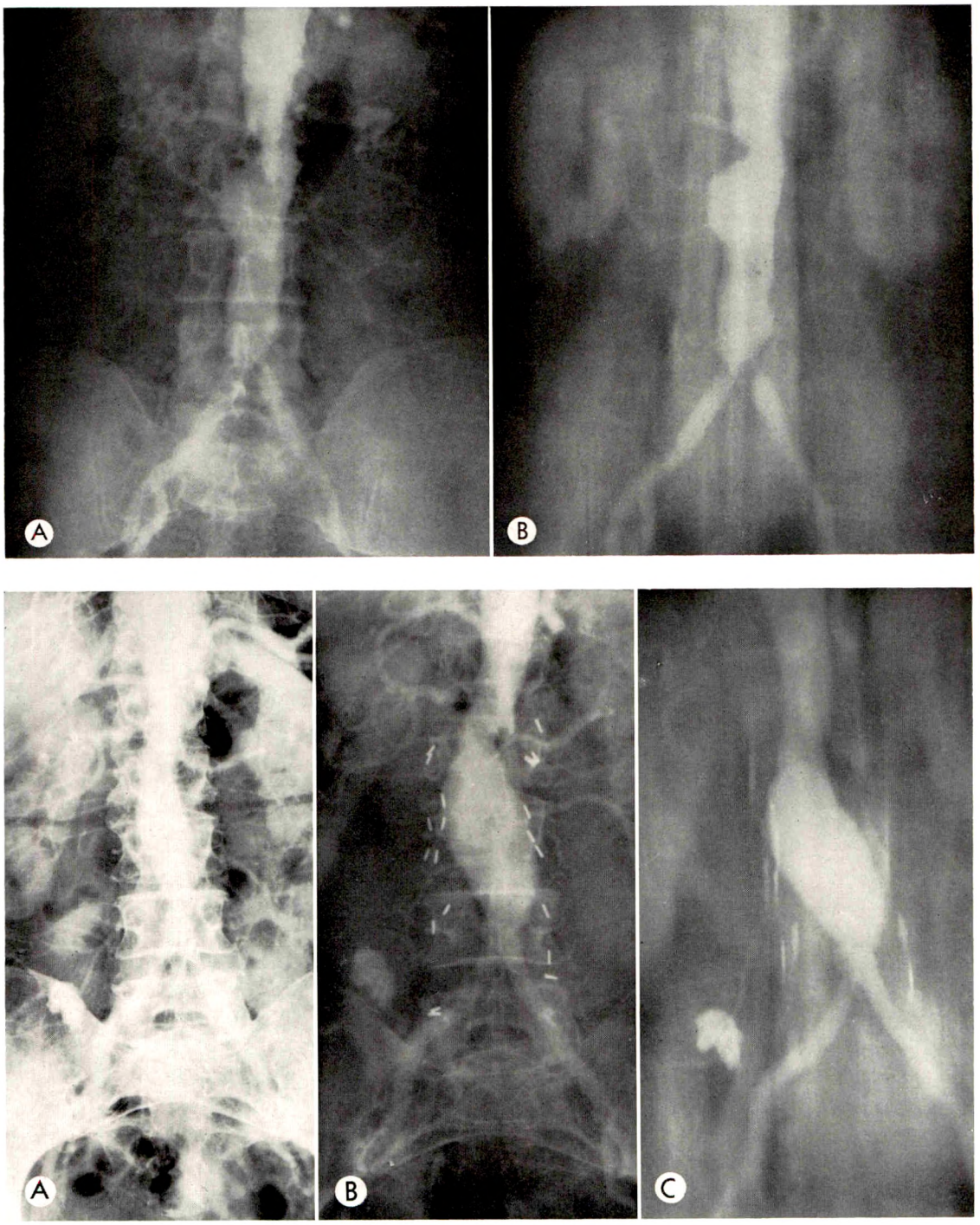


Fig. 10. In 1959, at the age of 52, a woman complaining of intermittent claudication of both legs had (*A*) a markedly irregular, tortuous and mildly aneurysmally dilated abdominal aorta. Both superficial femoral arteries (not shown here) were occluded in the lower thighs. (*B*) Bilateral lumbar sympathectomy failed to alleviate the symptoms. Indeed the aneurysm became larger in 1962. (*C*) Aortotomogram well demonstrates the abdominal aortic aneurysmal and occlusive disease with the severe, although intact, tortuosity of the aortoiliac arteries. Resection of the abdominal aortic aneurysm with replacement by a teflon graft and by-pass arms extending to the popliteal arteries bilaterally is planned.

other hand, when a thrombus complicates aneurysmal disease of the abdominal aorta, aortotomography enhances its demonstration (Fig. 9, *A* and *B*). Since the thrombus, in the above case, was in the vicinity of the right renal artery, the hypertension (170/80 mm. Hg) was correctly attributed to right renal artery thrombosis. Also, when occlusive and aneurysmal disease of the abdominal aorta coexist, many more details of the disease can be visualized after aortotomography. A patient with severe aortoiliac occlusive disease (Fig. 10*A*) had bilateral lumbar sympathectomy for palliation of bilateral intermittent claudication of both hips. Serial intravenous abdominal aortograms 3 years later showed that the aneurysm had increased in size and the aortoiliac constrictive disease had also persisted (Fig. 10*B*). Both these findings are clearly demonstrated in the aortotomogram (Fig. 10*C*).

DISCUSSION

Backlund[1,2] in 2 articles has reveiwed the literature and discussed the technique and advantages of simultaneous planigraphy. In this country the matched screen apparatus used for simultaneous tomography has become known as the book-cassette. It is very well suited for tomography of the opacified aorta, especially in arteriosclerosis, for the tortuous abdominal aorta and aortoiliac branches may reach varied depths so that only a single tomographic level may fail to show the details of the entire vascular system. Furthermore, the time of opacification of the abdominal aorta while greater than that of the thoracic aorta, will not permit more than 1 or 2 single exposures (cuts). In addition, the reduction in skin dose radiation provided by the book-cassette as compared to the multiple single cut tomography is an advantage. Furthermore, the simplicity of making a single simultaneous exposure of multiple roentgenograms makes it an easier technical procedure.[1,2]

Aortotomography, in this center, has been used only as an adjunct to conventional abdominal aortography and peripheral arteriography. If the abdominal aortic and aortoiliac artery is intact, the study is ended and the needles are removed from the arms. Since aortotomography requires a second injection of contrast medium, the question whether this is harmful may rightly be raised. Even though biplane angiocardiography was primarily advocated to obviate additional injections of contrast medium, the widespread use of multiple injections during cardiac catheterization in order to document the location of the catheter and for cineangiocardiography has disposed of the myth that repeat injections of contrast materials are dangerous. Furthermore, in this center for many years multiple injections for frontal, lateral and oblique views have been made without undue risk.[10] Even though 2 fatalities have occurred following simultaneous bilateral injection of concentrated contrast agents, death was attributed to drug sensitivity rather than allergy.[13] Indeed, death in one patient occurred immediately after the first injection; in the other it followed several hours after completion of the second injection.[15] Accordingly, it would appear that if indicated, there should be no hesitation to give a second injection for aortotomography.

Aortotomography by visualizing the abdominal aorta and aortoiliac system at various levels tends to overcome confusing shadows due to neighboring solid structures such as the spine, kidneys, liver and spleen. In addition, the gaseous contents of the gastrointestinal system may be differentiated from inherent occlusive disease (Fig. 8, *A* and *B*). Occlusive disease of the abdominal aorta and aortoiliac system may be especially difficult to recognize because of the underlying spine shadow (Fig. 1*B*, 2*B*, 3, 4*B*, 5*B*, 7, and 9*B*). Irregular, thrombus-lined aneurysms are also well delineated on aortotomograms (Fig. 6*B*, 7, 8*B*, 9*B*, and 10*C*). Finally, a study of the opacified abdominal aorta at 7 levels permits evaluation of disease of the other abdominal aortic branches such as of the

celiac axis and renal arteries. Intravenous abdominal aortic or aortotomographic visualization of the renal arteries for study of a renal arterial cause of hypertension cannot be expected to approach the degree of accuracy provided by the percutaneous transfemoral method of renal arteriography;[7] however, in abdominal aortic or aortoiliac occlusive disease, wherein the risks of dislodging an embolus, aortic dissection, or rupture are great, the intravenous method would appear to be more desirable. In such cases injection of the abdominal aorta via advancement of a brachial catheter may also, because of brachiocephalic arterial tortuosity and sclerosis, prove difficult. Incidentally, a patient in this series with a mesenteric arteriovenous fistula which followed small bowel resection presented a vaguely enlarged cluster of vessels in the region of the mesenteric artery on the aortogram. Definite diagnosis, however, required selective mesenteric arteriography.[17]

Since a series of 7 roentgenograms at varying levels are secured during aortotomography and because the study is done soon after the abdominal aorta is visualized, excellent nephrotomographic studies are routinely obtained. For the same reason, visualization of the liver and spleen is also secured (hepatotomography and splenotomography).

SUMMARY AND CONCLUSIONS

Aortotomography is the method of visualizing the intravenously opacified abdominal aorta by making a series of roentgenograms of the opacified aorta at varying levels (body-section roentgenography, planigraphy). A commercially available book-cassette device permits simultaneous filming after roentgen exposure with a standard tomographic apparatus.

In a series of 41 patients, aortotomography proved valuable for the refinement and precise localization of arteriosclerotic occlusive disease of the abdominal aorta and aortoiliac system. In abdominal aortic aneurysms, intraluminal and especially extraluminal thrombus was readily visualized. In addition, because the procedure was done after routine survey of the abdominal aortic and peripheral vascular system, visualization of the kidneys, liver, and spleen (nephrotomography, hepatotomography and splenotomography) was also secured.

Aortotomography and intravenous aortography are not recommended for diagnosis of renal arterial abnormalities in the case of suspected renal hypertension. Percutaneous femoral retrograde renal arteriography is superior for this. It has, however, proved valuable for visualizing renal arteries in patients who, because of occlusive or aneurysmal disease of the abdominal aortic, aortoiliac or brachial arteries, are high risk cases for arterial catheterization or puncture (translumbar aortography).

Because intravenous aortotomography enhances visualization of the abdominal aorta and aortoiliac branches by separating these structures from the underlying spine and neighboring gaseous and solid organs, it is highly recommended as a secondary procedure in selected cases in order to supplement conventional intravenous abdominal aortography.

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VOL. 89, NO. 2

CARDIAC VENTRICULOGRAPHY*

TRANSAORTIC CATHETER OPACIFICATION OF THE LEFT VENTRICLE

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WHILE selective catheter angiocardiography as introduced by Chávez *et al.*[3] permits localized opacification of the right heart chambers, it does not regularly achieve direct deposit of radiopaque medium into the left cardiac chambers. On occasion, the catheter may be passed from the right to the left side of the heart via a patent foramen ovale or a congenital septal defect.

The procedure of transthoracic needle puncture opacification of the left ventricle in humans, as first reported in 1936 by Nuvoli[13] and later, in 1951, by Ponsdomenech and Nunez[14] and others,[4,19] does permit direct opacification of the left ventricle. The most extensive considerations of this procedure have been those of Lehman and co-workers.[6,7,9,20,21] The hazards and complications incident to the performance of such a needle puncture opacification procedure in 350 patients were of such degree that the authors have abandoned the transthoracic needle puncture opacification type of study.

It is well evident that with certain pathologic entities there are definite indications for direct opacification of the left ventricle. That this can be accomplished by transaortic introduction of a catheter into the left ventricle has been established for some time. Practically all workers who have employed catheter thoracic aortography with positioning of the catheter in the ascending aorta have noted that, on occasion, the catheter would cross the aortic valve to inadvertently enter the left ventricle.

Utilizing either the open-end, thin-wall Lehman aortography catheter,* or the National Institutes of Health (NIH)* or Rodriquez Alverez closed-end, multiple side-hole catheters,* it has been our experience that intentional left ventricular entry across the aortic valve presented difficulty in a considerable proportion of attempts, and particularly in instances of aortic valvular stenosis.

Dotter[5] has recently described in detail the use of a Seldinger[18] type of percutaneous introduction of a catheter into a peripheral artery and the utilization of a spring guide to advance the catheter across the aortic valve into the left ventricle. This technique does require that the catheter have an open distal end, through which the guide is extended. In spite of the associated multiple side holes usually incorporated into the catheter near its distal end, there still remains some problem of jet injection and catheter recoil resulting from the end opening.

The Ross *et al.*[17] transseptal puncture technique and its modification as most recently described by McIntosh *et al.*[11] does allow entry of a needle, followed by a catheter, into the left atrium. It cannot, however, be expected that satisfactory catheterization of the left ventricle for rapid radiopaque injection can regularly be accomplished by the Ross type of procedure.

In an effort to avoid the use of an open-end catheter with its end-jet effect and possible catheter recoil and to effect an increase in the percentage of successful

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entries into the left ventricle even in patients with aortic valvular stenosis, several years ago one of us (J.S.L.) devised a catheter to be used specifically for left ventricular catheter opacification study. This catheter has now been used in 100 consecutive cases. Our experiences in these 100 examinations, the details of the catheter, and the technique employed form the basis of this report.

VENTRICULOGRAPHY CATHETER

The ventriculography catheter has the same thin-wall construction as does the so-called Lehman aortography catheter. For adult application, the catheters* have been produced in sizes F6, F7 and F8, in 80 and 100 cm. lengths. The terminal 3.5 cm. tapers to a size approximately F4. This tapered portion has no lumen, but is filled in with a radiopaque substance. Two sets of opposing side holes at right angles to each other open into the distal portion of the catheter lumen, approximately 4.0 cm. from the catheter tip. For pediatric usage, catheters are identical to the adult type, except that they are of sizes F5 and F6, and of 50 and 80 cm. lengths, with the closed lumen tapered extremity 3.0 cm. in length.

The design of this catheter was based upon our observations that with the NIH or similar catheters advancement down the ascending aorta with intent to cross the aortic valve usually resulted in the catheter tip entering one of the aortic sinuses. When penetration of the left ventricle was achieved, it was usually effected by the distal portion of the catheter being forced into a U-shaped bend, with the catheter then snapping across the aortic valve cusp(s). It was our observation that in human patients such localized bending of the distal end of the catheter was not regularly accomplished even despite repeated attempts at slight withdrawal and re-advancement of the catheter. It is noteworthy that this "bending" of the catheter was much more regularly accomplished in experimental animals (dogs).

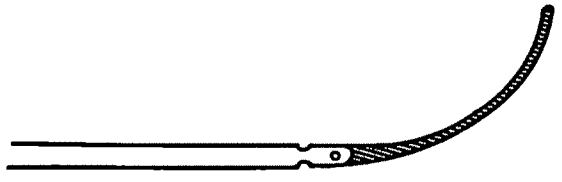


FIG. 1. Diagram of cardiac ventriculography catheter.

The purpose of the design was, therefore, to provide a more flexible distal portion of the catheter, the tapered portion readily forming a U-shaped bend, yet retaining a catheter lumen large enough to permit rapid radiopaque medium injection and, at the same time, to avoid end-jet effect and recoil. Details of the catheter are shown in Figures 1 and 2.

METHODS, MATERIALS AND TECHNIQUES

The procedure of cardiac ventriculography requires team work. It is our belief that it should be under the supervision and direction of the radiologist. Since the catheter for this particular type of procedure is introduced directly into a peripheral artery, the team should include personnel trained in the techniques of arterial exposure, arteriotomy, catheter introduction and manipulations, and vascular repair.

Continuous electrocardiographic monitoring is mandatory and, since pressure recordings from the aorta and left ventricle add important information, appropriate personnel conversant with electrocardiographic and manometric apparatus is hence required.

Equipment and medications which may be necessary in the event of any complications, such as protracted arrhythmias or cardiac arrest, must be at hand.

General anesthesia is not necessary, except perhaps in infants and small children. Preoperative medication with a barbiturate and demerol has been routine.

For the opacification study, we prefer the diatrizoate compounds of moderate iodine content and moderate viscosity over the higher-iodine content and more viscid

media.[8] For the average adult, we have established our dosage at 50 cc. per injection and do not hesitate to make one or two additional injections as required. In children, we have varied the injected dose according to body weight, roughly along the lines of 0.3 to 0.5 cc. per pound of body weight.

It is important that the radiopaque medium be injected as rapidly as possible, with the total injection time not exceeding 2 seconds, and preferably less. In order to achieve the most rapid injection, it is essential that the catheter be of the largest lumen and shortest length practicable.

A pressure injector capable of delivering the entire dose of radiopaque medium through the selected catheter and into the left ventricle in 2 seconds or less is of prime importance.

Film recording may be by either direct filming or cineroentgenography. If direct filming is used, it is essential that it be serial and rapid. It has been our observation that with serial filming at rates of 2 per second, certain important information may not be recorded adequately, particularly movements of valve leaflets or cusps. We prefer filming rates of 4 to 6 per second, with filming carried for 5 seconds. Exposure times should not exceed 1/20 second, and ideally should be of shorter duration. Except for patients of very large habitus, we utilize either 1/60 or 1/120-second exposures, with corresponding adjustment in kilovoltage and milliamperage factors.

Cineroentgenography is a satisfactory method of recording in cardiac ventriculography. We have used 16 mm. cine recording, and consider that in some respects it has certain advantages. The dynamic events of valve motion and jets of regurgitant opacification are dramatically portrayed by cineroentgenography. On the other hand, our observations are that, at least with present equipment, the portrayal of smaller detail is somewhat less revealing on cine studies than on direct serial filming. Occasionally, we have used

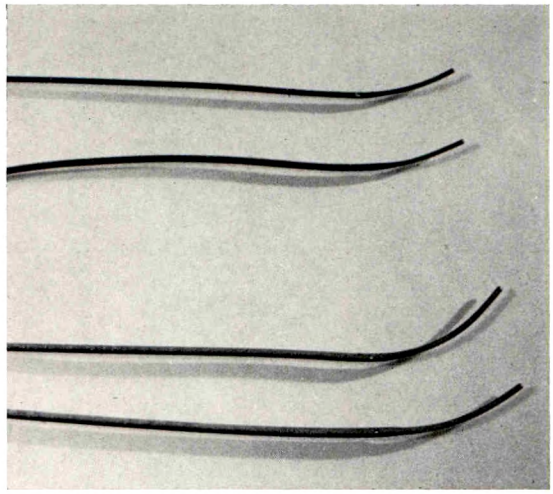


Fig. 2. Cardiac ventriculography catheters. The upper 2 catheters are sizes F5 and F6 for use in children. The lower 2 catheters are sizes F7 and F8 for use in adults.

cineroentgenography, and followed this by direct serial roentgenography which, of course, involves repetition of radiopaque injection, but which has provided both a dynamic motion study and a study revealing maximal detail.

In general, the most informative projection is the lateral one. Certainly, in the demonstration of radiopaque passage from the left ventricle through the mitral valve into the left atrium, in cases of mitral insufficiency, the lateral projection affords the best opportunity to assess the degree of mitral regurgitation. The aortic valve is also well demonstrated in lateral study. Coronary arterial visualization, particularly of the right coronary artery, may, however, be somewhat obscured by the superimposed left ventricular opacification.

In the study of left ventricular aneurysm, one must decide which projection is most likely to provide the greatest amount of information regarding the suspected or definitive lesion. Usually, our most reliable information regarding the demonstration of a left ventricular aneurysm has been obtained from an anteroposterior projection. At times, both anteroposterior and lateral pro-

jections have been employed to advantage, of course involving (in the absence of simultaneous biplane roentgenography) a repetition of the left ventricular injection.

Interventricular septal defects are best demonstrated in the right posterior (or left anterior) oblique projection, which places the interventricular septum in axial line with the roentgen-ray beam.

It has been our general rule to employ a lateral projection for cardiac ventriculography study unless considerations regarding the suspected pathologic entity dictate the advisability of other projections.

The anteroposterior projection is generally preferable for the frequently associated catheter thoracic aortography study.

In all of the present series, the catheter has been introduced into either a brachial artery at the elbow, or a femoral artery just distal to the inguinal ligament. This has required cut-down exposure and mobilization of a sufficient length of the selected artery.

We have usually used a short, longitudinal arteriotomy incision. The catheter is introduced and advanced, with manipulation under fluoroscopic control, to the ascending aorta. With continuous electrocardiographic monitoring, the catheter is then further advanced to the level of the aortic valve. Some backward bending of the tip of the catheter as it engages in one of the aortic sinuses is to be expected, and this 'bending' of the tip usually causes the catheter to snap across the aortic valve cusp and enter the left ventricle.

Occasionally, the catheter tip may enter a coronary artery. On a number of occasions, we have observed passage of the catheter for some distance down a coronary artery. Recognition of this inadvertency is important, and can be determined by careful fluoroscopic (image amplification) observation. The catheter should, of course, be withdrawn immediately.

When the catheter enters the left ventricle, some cardiac arrhythmia is usually noted, as will be described later. Manipulation and adjustment of catheter position to effect relief of the arrhythmia are important steps. With the catheter properly positioned in the left ventricle, the radiopaque injection is made with simultaneous roentgenography. We advocate starting roentgenography immediately before the injection, in order that at least one control or scout roentgenogram will be available for comparison with those showing the opacification. Following the left ventricular opacification, it is our usual custom to then obtain pressure recordings from the left ventricle via the catheter. With continuous pressure trace recording, the catheter is then pulled back across the aortic valve until aortic pressures have been recorded.

It is our not infrequent custom to then withdraw the cardiac ventriculography catheter and introduce an NIH type catheter, positioning its tip immediately above the aortic valve for catheter thoracic aortography. Such a supravalvular opacification study is regularly employed when we are interested in the status of the aortic valve and a determination of the presence or absence of aortic insufficiency, or when coronary arteriography is also desired.

Upon withdrawal of the catheter, the arteriotomy is meticulously repaired, with every effort made to avoid any luminal narrowing at the arteriotomy site.

We consider it advisable to administer intravenous heparinization immediately prior to the procedure, and to then neutralize the heparin by intravenous administration of protamine at the termination of the procedure.

ANALYSIS OF CASES AND RESULTS

An analysis of the 100 cases in our series reveals that 55 patients were males, and 45 females. There were no infants or young children. The youngest patient was 11 years old; the oldest, 62 years. Table I shows the age distribution by decades.

The primary purposes of the procedure are shown in Table II. A consideration of each of these objectives is covered in the Discussion of this paper.

Table I

LEFT CARDIAC CATHETER VENTRICULOGRAPHY

(100 Cases)

Age Distribution	
10 to 19 years	13
20 to 29 years	17
30 to 39 years	27
40 to 49 years	28
50 to 59 years	14
Over 60 years	1

The site of catheter introduction was the right brachial artery in 91 examinations; the left brachial in 3; the right femoral in 5, and the left femoral in one. The right brachial artery was preferred as the artery of easiest access, with most direct continuity with the ascending aorta. In all instances, the catheter was advanced to the ascending aorta, although there were 3 occasions wherein some difficulty was encountered in passage of the catheter from the right brachial artery because of tortuosity and kinking of the subclavian or innominate artery. On these occasions, it was necessary to withdraw the catheter and re-introduce another of different size or tip curvature. No remarkable difficulty was experienced in catheter transit from the femoral artery to the ascending aorta except for a few occasions when the initial catheter, in its passage into the aortic arch, would persistently enter one of the brachiocephalic vessels. On these occasions, substitution of a catheter of slightly different tip curvature (either an older or a newer catheter) was necessary.

The ease of passage of the catheter across the aortic valve varied. In 66 of the 100 examinations, not the slightest difficulty was experienced, the catheter either snapping promptly across the aortic valve or, less frequently, entering the left ventricle without appreciable bending of the tip. Slight difficulty, requiring several catheter manipulations (slight withdrawal and re-advancement) was encountered in 7 patients. There was moderate difficulty in left ventricular entry in 13 patients. Marked difficulty was experienced 4 times, and there was complete failure to enter the left ventricle in 10 examinations. Thus, there was a 10 per cent incidence of failure to accomplish catheterization.

It should be emphasized that attempts to enter the left ventricle were never abandoned until at least 2 or more ventriculography catheters had been tried. On one occasion, 7 catheters were employed before attempt at left ventricular entry was discontinued. In several of the cases of moderate and marked difficulty in left ventricular catheterization, it was necessary to utilize more than one catheter before successful entry was achieved.

Aortic valvular stenosis might be expected to present problems of transvalvular passage. Indeed, of the 10 failures, 7 had reliable clinical evidence of aortic stenosis. It is, however, noteworthy that of these 7 failures, apparently due to the presence of aortic stenosis, 5 showed evidence of associated dynamic aortic valvular insufficiency with regurgitant opacification of the left ventricle on supravalvular opacification study. Of the other 3 failures, 2 had reliable evidence of aortic valvular insufficiency; the other presented no evidence of aortic valvular disease, but did have mitral stenosis, which we do not believe influenced at all the problem of catheter passage across the aortic valve.

With regard to aortic valvular stenosis in relationship to transaortic left ventricular

Table II

LEFT CARDIAC CATHETER VENTRICULOGRAPHY

(100 Cases)

Purpose of Examination	
Evaluate for:	
Mitral Valvular Disease (M I)	40
Aortic Valvular Disease	23
Mitral and Aortic Valvular Disease	25
Left Ventricular Aneurysm	4
Interventricular Septal Defect	3
Other Congenital Heart Disease	4
Aortic Sinus Fistula	1

catheterization, it is interesting to note that of the total series of 100 cases, there were 26 with varying degrees of aortic stenosis. In 19, successful entry into the left ventricle was achieved, with no difficulty being encountered in 12, slight difficulty in 2, moderate in 3, while marked difficulty was experienced on 2 occasions. Of these 19 cases, determinations of pressure within the left ventricle and during pull-back of catheter across the aortic valve to the ascending aorta were recorded in all but one. The recorded systolic pressure gradient across the aortic valve in these 18 cases of successful catheterization of the left ventricle in the presence of aortic valvular stenosis varied from 15 to 110 mm. Hg. The two highest systolic pressure gradients were 90 mm. Hg, and in this case there was but slight difficulty in catheterization of the left ventricle, and 110 mm. Hg, wherein there was marked difficulty.

As previously mentioned, entry of a catheter into the left ventricle rather regularly produces some alteration in cardiac rhythm. The presence of a foreign body (catheter) touching the endocardium of the left ventricle can be expected to produce an ectopic focus of stimulation of the ventricular myocardium. This may be in the form of a single, or a number of intermittent ventricular extrasystoles. Not infrequently, short runs of ventricular tachycardia will be observed. The potentiality of development of ventricular fibrillation (if persistent, a lethal arrhythmia) must be constantly borne in mind. This, of itself, emphasizes the absolute necessity for electrocardiographic monitoring throughout the procedure. On the occasion of development of persistent ventricular extrasystoles and, particularly, a run or runs of ventricular tachycardia, it is mandatory that there be immediate adjustment and manipulation of the catheter to a position that no longer induces such arrhythmia. A slight turn or twist of the catheter, or its slight withdrawal from contact with the particular area of the left ventricular endocardium, usually suffices to change the situation.

While any catheter-induced arrhythmia should be looked upon as important and of potentially serious significance, it is at the same time important to understand that some degree of momentary arrhythmia is to be expected when a catheter enters the left ventricle. Unless there is a constant persistence of ventricular premature contractions or ventricular tachycardia on careful manipulation of the catheter, we do not elect to withdraw the catheter from the left ventricle, and we do proceed with the cardiac ventriculography study. It is obviously of import that the procedure be accomplished as rapidly as possible once the catheter has entered the left ventricle, and that removal of the catheter from the left ventricle be achieved as soon as possible. Occasionally, catheterization of the left ventricle may be performed without *any* induced arrhythmia or aberration of the electrocardiographic tracing. We have 5 such instances in this series, where catheter entry and positioning in the left ventricle were made without occurrence of even one ventricular extrasystole. However, in the majority of instances, during the injection of the radiopaque medium into the left ventricle, an arrhythmia will be noted. This usually is in the form of a very short run of ventricular premature contractions and is usually followed by a short period of sinus conducted bradycardia with a following period of sinus conducted tachycardia. At the time of entry and during the transit of the radiopaque material through the coronary arterial system, varying degrees of S-T segment and T-wave change are usually noted. These are of brief duration, rarely lasting more than 5 seconds.

It is quite possible that in a particular circumstance a fatal arrhythmia may be immediately induced on entry of a catheter into the left ventricle. In this present series we have had one occasion of ventricular fibrillation. This was our one fatality and will be described in a following paragraph.

Analysis of the complications discloses that there were 2 instances involving problems at the site of the arteriotomy incision.

In the first, there was complete brachial artery occlusion, resulting in some light ischemic weakness of the right arm with, however, no permanent sequelae. The second involved femoral artery injury, with subintimal hematoma, which required a surgical transection and end-to-end anastomosis, with subsequent restoration of femoral artery flow and no sequelae.

The only other complication was the fatality just mentioned. This occurred in the 92nd case of this series, in a young adult who presented clinical evidence of severe rheumatic multivalvular disease, with combined stenosis and insufficiency of both the aortic and mitral valves. The initial steps of cardiac catheter ventriculography proceeded without incident until the catheter entered the left ventricle. The transaortic passage was accomplished with no difficulty, but at the instant the catheter entered the left ventricle, ventricular fibrillation was noted. Immediate opening of the chest, cardiac massage and electrical defibrillation, along with intratracheal intubation for controlled oxygenation failed to establish return of effective cardiac pulsation, and the patient succumbed. This case is the only fatality in our 100 case series.

DISCUSSION

Left cardiac catheter ventriculography has had, in our hands, its widest application in the evaluation of rheumatic mitral valvular disease, particularly in the demonstration and quantitation of mitral valvular insufficiency. Of the 100 cases comprising this report, the primary purpose of the examination was an evaluation of mitral insufficiency in 40. The procedure was employed primarily for study of the aortic valve in 23. In these latter instances, left ventricular opacification was in some measure incidental to a catheter thoracic aortography procedure and was accomplished just prior to determinations of

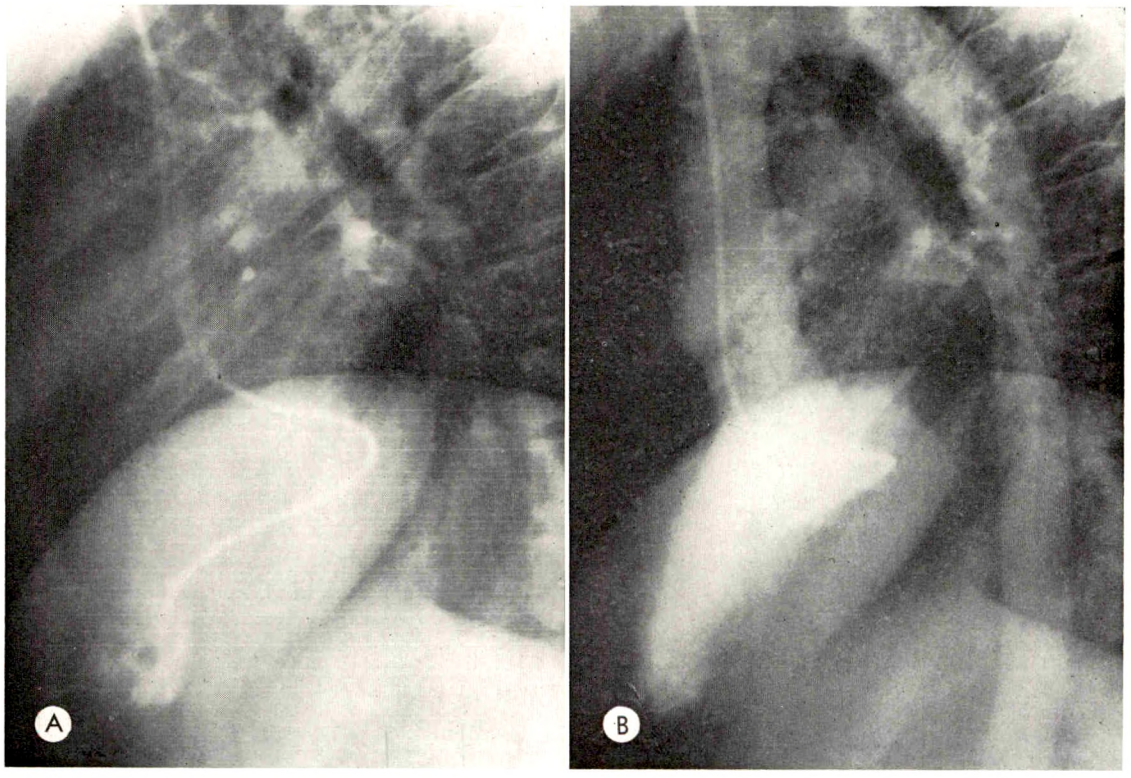


Fig. 3. Cardiac ventriculograms. No mitral insufficiency. (*A*) Beginning of radiopaque injection. (*B*) Completion of injection. No evidence of radiopaque reflux into the left atrium.

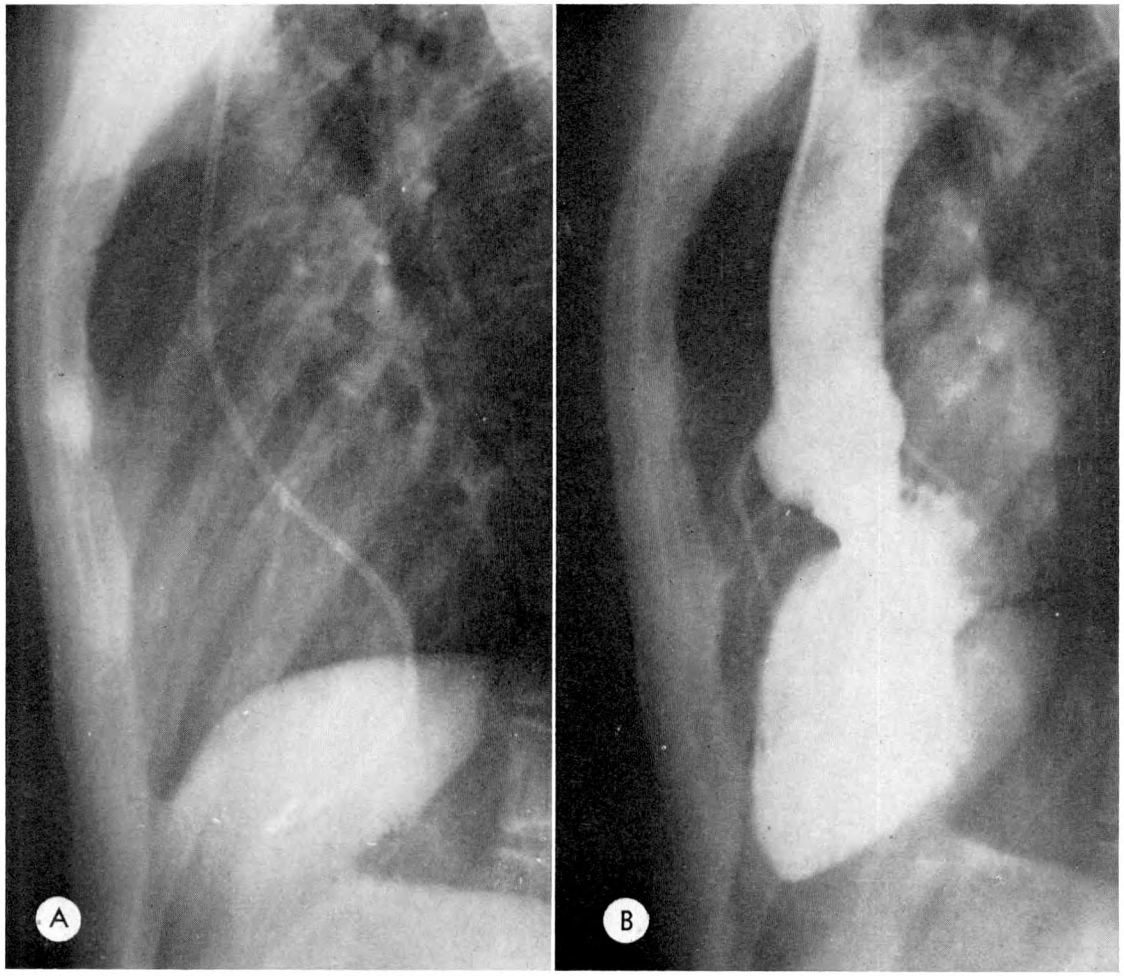


FIG. 4. Cardiac ventriculograms. One plus mitral insufficiency. (*A*) Immediately before radiopaque injection. (*B*) Completion of injection. Slight reflux into left atrium.

pressures within the left ventricle, catheter pull-back across the aortic valve and pressure recordings from the ascending aorta. In 25 examinations, the basic intent of the procedure was evaluation of both the mitral and aortic valves. On 4 occasions, considerations of a left ventricular aneurysm prompted the left ventricular study. In the remaining 8 cases, it was for evaluation for interventricular septal defect in 3, other congenital heart disease in 4, and aortic sinus fistula was the primary purpose in one.

In previous publications originating from our Institution,[6,7,9,20,21] the usefulness of direct opacification of the left ventricle in the demonstration and quantitation of mitral insufficiency has been discussed. Our further studies, such as the cases comprising this report, convince us that the competent mitral valve will not permit significant regurgitant opacification of the left atrium under the conditions of left ventricular opacification as we employ it. We have observed that on rare occasions of momentary bradycardia or asystole, a puff or two of opaque medium enters the left atrium in the presence of a competent mitral valve.

It is our experience that left cardiac ventriculography is a reliable procedure for the diagnosis of mitral insufficiency. The quantitation of such insufficiency by this procedure is admittedly only a rough esti-

mation. This estimate, however, carries considerable weight with our cardiologic and surgical colleagues. Figures 3 to 7, inclusive, illustrate absence and several degrees of mitral valvular insufficiency (Grades 1 to 4 plus).

In a considerable majority of our 100 cases, we elected also to make a study of the ascending aorta and the aortic valve and, on some occasions, also of the coronary arteries by supravalvular radiopaque injection into the ascending aorta in the manner of catheter thoracic aortography. In most of these, such additional thoracic aortography study was employed to determine, insofar as possible, any evidence of aortic valvular deformity in the nature of thickened aortic valve cusps, lack of normal mobility of the cusps, and the presence and degree of any existing aortic valvular insufficiency. While evaluation of aortic valve deformity, cusp thickening and distortion, and degrees of mobility of the cusps may be partially achieved by a left ventricular opacification study, one obtains more complete information regarding the status of the aortic valve when such a study is combined with a catheter thoracic aortography procedure. Certainly, any estimation of aortic valvular insufficiency by roentgenologic study requires supravalvular opacification. Determination of the presence and degree of aortic valvular stenosis is accomplished by pressure recordings via the catheter.

We employed such a double procedure study in all but one of the 19 cases of successful left ventricular study in the presence of aortic stenosis, and noted that deformity of the aortic valve was evident in all but one. A report now in press, regarding the demonstration and quantitation of aortic valvular insufficiency, will elaborate further on the roentgenologic findings in aortic valvular disease.

In our previous experience with the

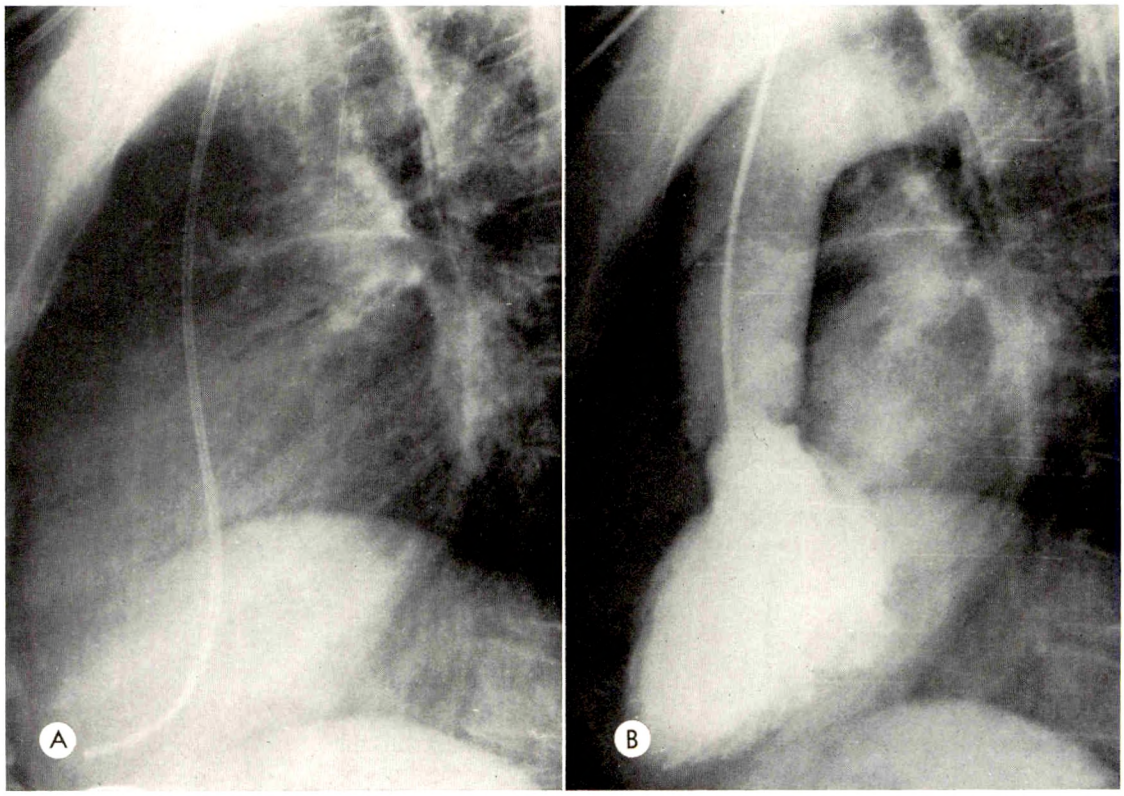


Fig. 5. Cardiac ventriculograms. Two plus mitral insufficiency. (*A*) Immediately before radiopaque injection. (*B*) Completion of injection. Moderate reflux into left atrium.

transthoracic left ventricular needle puncture type of cardiac ventriculography, we have had the temerity to make direct radiopaque needle injection opacification of the left ventricle in a number of patients with left ventricular aneurysm. While we had no instance of any complication in these cases, it must be recognized that such procedure is hazardous. Nevertheless, the information derived was of decided value in localizing the degree and extent of such aneurysms and was of vital importance to our surgical colleagues in their considerations regarding the advisability of surgical resection of the aneurysms.

In our present series, we have but 4 cases where a left ventricular aneurysm was under consideration. In 2, there was definite evidence of aneurysm; the other 2 were finally considered by all combined clinical and roentgenologic evidence to have no indication of aneurysm. The positive diagnoses are illustrated in Figures 8 and 9.

We believe that in cases of questionable diagnoses and in patients in whom aneurysm resection is contemplated, cardiac ventriculography is generally indicated. The likelihood of rupture of an aneurysm during left ventricular injection seems rather remote. Perhaps the only real danger is the unlikely possibility of thrombus dislodgement during catheter manipulation in the left ventricle.

An interventricular septal defect may be demonstrated readily by direct left ventricular opacification. Estimations of the location and size of the defect are possible. Cardiac ventriculography appears well indicated for the evaluation of such congenital defects. In all of our 3 cases, cineroentgenography was the method of recording, and since cine frames do not lend themselves to good reproduction, we have not included any illustration of our cases in this publication.

Left cardiac ventriculography has defi-

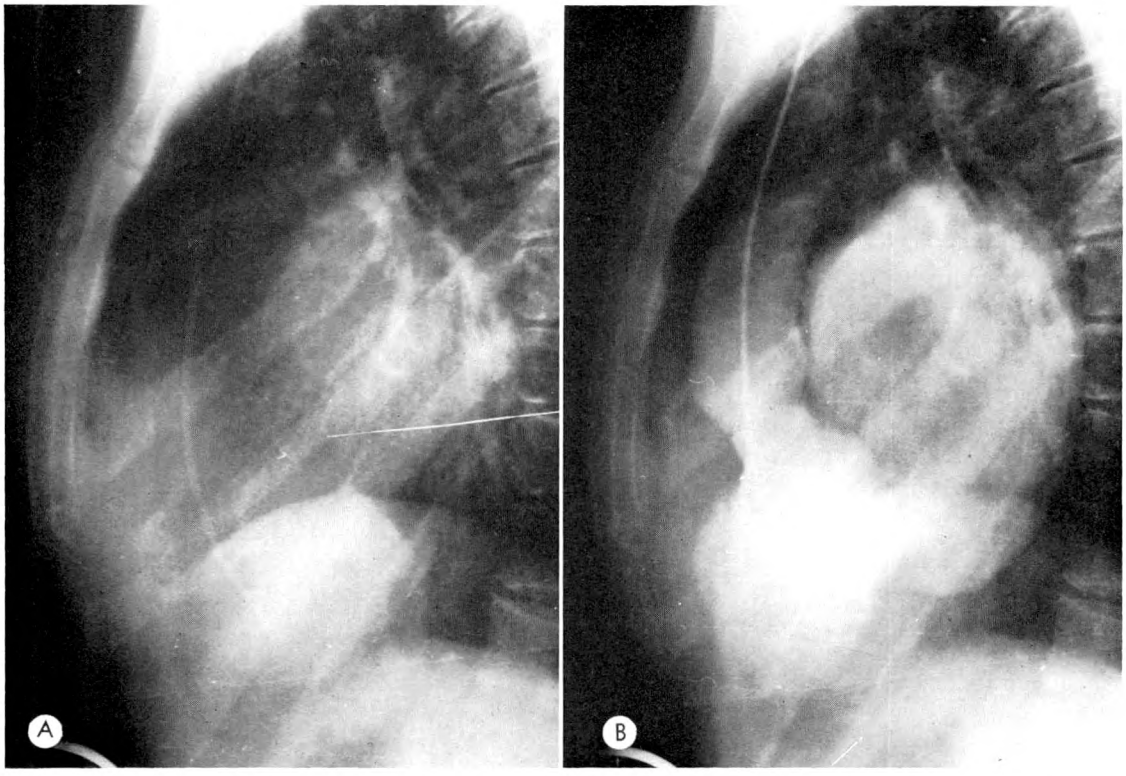


FIG. 6. Cardiac ventriculograms. Three plus mitral insufficiency. (*A*) Immediately before radiopaque injection. (*B*) Completion of injection. Marked reflux into left atrium.

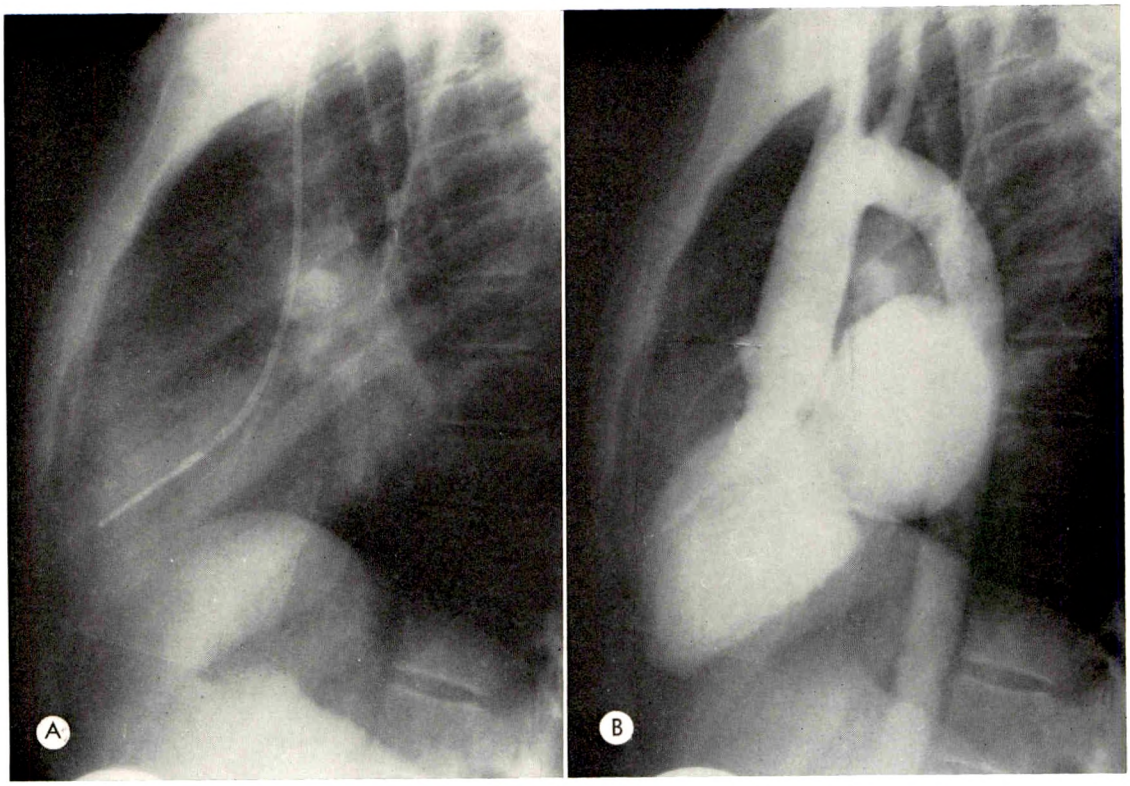


Fig. 7. Cardiac ventriculograms. Four plus mitral insufficiency. (*A*) Immediately before radiopaque injection. (*B*) Completion of injection. Massive reflux into left atrium.

nite applications to a number of other congenital malformations of the heart. We have used it for the diagnosis of fibroelastosis, noting on cineroentgenography a lack of normal left ventricular contractions.

Observations in corrected transposition of the great vessels should prove interesting. We have had no recent opportunity to study such an entity by cardiac ventriculography.

In the single case of aortic sinus fistula, the most vital information was obtained by the additive procedure of catheter thoracic aortography. This case will be reported in a subsequent publication.

No mention has been made, thus far, of the findings in mitral stenosis. We have ob-

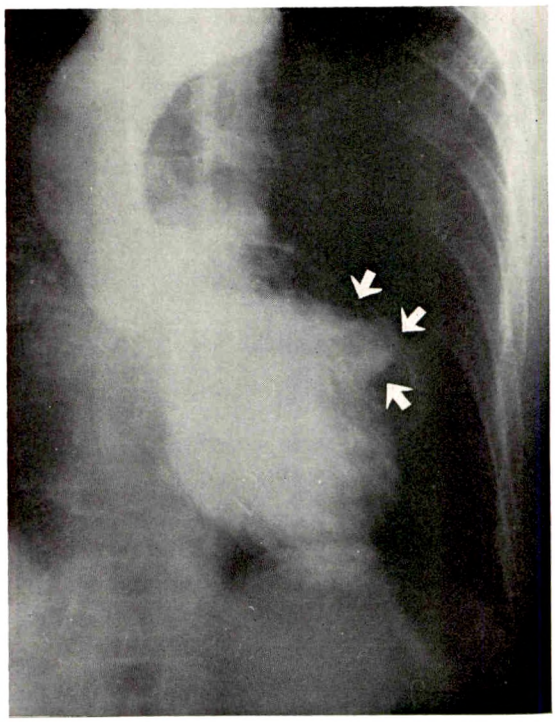


Fig. 8. Cardiac ventriculogram. Left ventricular aneurysm. Note localized left lateral pocket of the aneurysm (arrows).

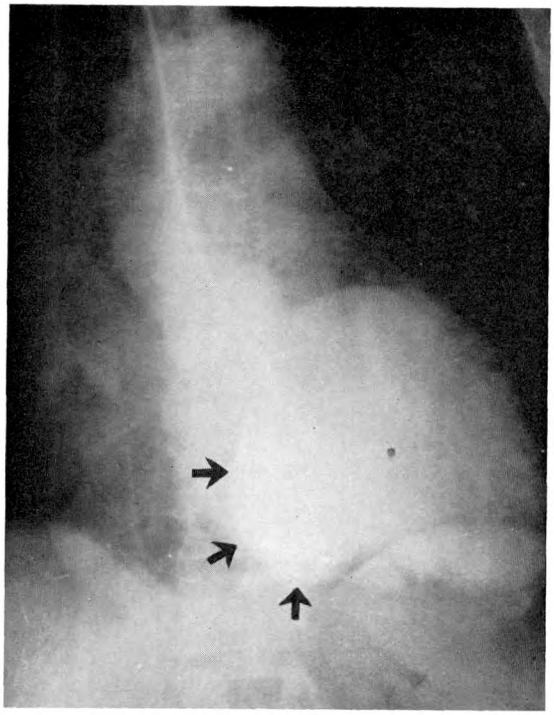


FIG. 9. Cardiac ventriculogram. Left ventricular aneurysm. Note right marginal extension of the ventricular lumen (arrows). It was indeterminate whether this aneurysm involved the septum.

served the doming of the mitral valve reported by Arvidsson.[1] Certainly, continued studies of mitral valve function by cardiac ventriculography may add to our information regarding the pathophysiology of mitral valvular disease.

FURTHER CONSIDERATIONS

This presentation has been confined to experiences with a new catheter designed for left ventricular catheterization and opacification. Its introduction into the arterial system and thence to the left ventricle requires exposure of a peripheral artery, arteriotomy, and subsequent arterial repair. Such a procedure is time-consuming and requires surgical skills, particularly if a low incidence of complications at the site of catheter insertion is to be maintained.

The techniques of percutaneous catheterization of peripheral arteries with positioning of the catheter in the aorta and in arteries originating from the aorta have been well described in the medical literature.[5,17,18] Transaortic catheterization of the left ventricle by a percutaneous peripheral artery catheter insertion has also been described.[2,5,10,11,15,16] Our own personal experiences with such techniques for cardiac ventriculography have been limited.

The recent publication of McIntosh and co-workers[11] reports success in retrograde catheterization of the left ventricle, with a catheter of adequate internal diameter to give a dependable undamped pulse contour, and utilizing a peripheral percutaneous approach, in 176 of 182 patients without aortic stenosis. These investigators employed a needle and stylus for the femoral artery in the manner of the Seldinger technique, and introduced an F7 or F8, 100 cm. Lehman catheter (or, less frequently, a carefully measured 100 cm. length of PE 240 or 260 polyethylene tubing). They state that "crossing a stenosed aortic valve is frequently difficult or impossible."

It has been our observation that brachial artery catheterization, using the Seldinger technique, will not usually permit introduction of a catheter of sufficient size to achieve adequate injection opacification of the left ventricle. We have further noted that brachial artery catheterization is more difficult than catheterization via the femoral artery. At the same time, we have a definite conviction that manipulation of a catheter across the aortic valve (particularly a stenosed valve) is easier by a brachial than a femoral artery approach.

Catheter length, catheter bending and looping proximal to the ascending aorta, ease of advancement and manipulation of the catheter tip both at the level of the aortic valve and within the left ventricle (important as regards avoidance of hazardous catheter-induced cardiac arrhythmias) are weighty considerations in the percutaneous femoral artery approach.

The relative simplicity and absence of necessity for arterial exposure in a percutaneous catheter introduction have much merit and appeal. When the percutaneous technique can be employed successfully, we believe it to be the method of choice.

Failing to accomplish a desired left ventricular opacification study by a percutaneous technique, one may then have recourse to the employment of the technique and catheter procedure described in this communication.

SUMMARY

1. Considerations regarding direct opacification of the left ventricle (cardiac ventriculography) are discussed.

2. A new type of cardiac ventriculography catheter is described.

3. Experience with this catheter in 100 consecutive examinations is presented.

4. The values, applications and technical problems of cardiac ventriculography are considered.

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AN INQUIRY INTO THE PHYSICAL FACTORS GOVERNING THE FLOW OF CONTRAST SUBSTANCES THROUGH CATHETERS*

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EXPERIENCE[2,4,5] has shown that in the performance of selective angiography in adults it is desirable to inject a total of 18 to 20 gm. of iodine at a rate of 10 to 14 gm./sec. This implies a flow rate of 20 to 25 cc./sec. using the currently available contrast substances (content about 40 to 45 per cent iodine). Hamilton and Weldon[3] found that in so-called antegrade aortography and arteriography a flow rate of less than 14 gm. of iodine/sec. in adults was unsatisfactory. In children, lesser flow rates may suffice but even here flow rates of 20 cc./sec. seem desirable.

Flow rates using a large range of catheters, contrast substances, and pressures have been published.[3,5,7,10] When the flow rates of a particular contrast substance are plotted against pressures on linear graph paper, curves of similar contour are obtained, which are obviously nonlinear. Rodriguez-Alvarez and Rodriguez[10] and Lehman and Debbas[7] suggest that flow rates of fluids through small tubes should obey Poiseuille's formula; they both remark that this law holds for laminar type flow. However, they did not investigate the circumstances under which laminar flow would result, nor what factors govern flow rates when this laminar behavior ceases to exist.

An inspection of Poiseuille's formula (see below) shows that the catheter diameter or radius is the single most influential factor governing the flow rate and, of course, in a practical situation size is limited by the blood vessel into which the catheter must be inserted. Assuming a fixed catheter size and length, the other factors, namely pressure and viscosity, are of linear effect. Dotter and Straube[2] and Lehman and Debbas[7] have measured the viscosity of most of the available contrast substances. If Poiseuille's formula were applicable, the iodine content in relation to the viscosity of the contrast substance, namely iodine in gm./cc. divided by viscosity would give an index that would have a linear relationship to the flow rate of iodine through a catheter. This would lead to the following rating of contrast substances:

Contrast Substances	C/η
Hypaque 50%	12.8
Urokon 70%	10.7
Miokon 50%	10.6
Diodrast 70%	9.0
Ditriokon	7.7
Renografin 60%	7.5
Renovist	6.1
Renografin 76%	4.1
Miokon 90%	2.0

C = concentration of iodine
η = viscosity in relative units

In this paper we have investigated the applicability of Poiseuille's law to flow rates as encountered in selective angiography and also what description of flow rates can be given under circumstances where Poiseuille's law is no longer valid. This might lead to a different criterion for the rating of contrast substances.

MATERIALS AND PROCEDURES

We have measured the flow rates for a number of different opaque materials. Several properties of these materials are shown in Table 1.

The densities were determined by averaging a value obtained by weighing 2 cc. of the contrast substance and a value obtained with a hydrometer.

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Table I

Contrast Substance	Viscosity*** in cp	Densities in kg./cubic meter	Iodine Content** in gm./cc.
Renografin 60%	3.92*	1,318	0.293
Urokon 70%	4.3*	1,452	0.460
Ditriokon	5.2	1,413	0.400
Renografin 76%	9.1*	1,408	0.370
Miokon 90%	22	1,481	0.450

* The values for the viscosity marked by an asterisk were those as published by Lehman and Debbas.[7] Dotter and Straube[2] have given slightly different values for most of these substances at 37.5° C.

** Iodine content obtained from brochure furnished by manufacturer.

*** See Reference 12 for method of determination.

Contrast substances were stock solutions.* Temperature was obtained by heating these solutions before aspiration in a water bath and was maintained by the water jacket on the Gidlund pump and also a water bath around the receptacle in which the contrast solutions were injected. Temperature control at 37.5° C. was ±2°. The contrast substance was re-used for a total of at least 3 injections for each given set of factors. The timing of the injection was obtained by an electrical timer, accurate to approximately .01 second.

The internal diameter of the catheters was measured (Table II). For the Kifa catheter we used a volume determination using mercury and one with a microtome section measured under a microscope.

The diameter of a No. 7 Lehman open end catheter† is given by the manufacturer as 1.47 mm.; we found it to be 1.44 ± 0.04 mm. by a direct measurement of the lumen under the microscope.

The gauge of the Gidlund pump reads the pressure in kg./cm.^{2}. However, this is not the pressure in the injection cylinder due to the fact that 2 coupled pistons form an intermediate device. Since the ratio of these piston diameters is 2.2 (cross-section 7.8 cm. and 3.54 cm.), the pressure inside the injection cylinder would be 4.84 kg./cm.^{2} for each kg./cm.^{2} as read on the gauge; this would be equal to 68.8 lb./in.^{2} for each kg./cm.^{2}. (One can write this also as $2.2^2 \times 9.8 \times 10^4$ newton/m.^{2} for each kg./cm.^{2} as read on the meter dial.) Thus, the pressure inside the injection cylinder varied between approximately 140 lb./in.^{2} and 700 lb./in.^{2}. The pressures have been adjusted for a standard catheter length of 1 m.

* Miokon 90% and Ditriokon currently supplied by the Mallinckrodt Institute.

† Manufactured by U. S. Catheter Company, Glens Falls, New York.

Results and Discussion

Flow rates were plotted against pressure on logarithmic paper for each catheter and are presented in Graphs 1 through 4. Logarithmic paper was chosen since it was expected that this would lead to straight lines. In the analysis of these data, it is seen that Poiseuille's law in most instances is not applicable in the area of interest. Only for Miokon 90% and partly for Renografin 76% is the flow directly proportional to the pressure (p) as one sees from the 45° slope on the logarithmic paper. In these cases, we deal with so-called laminar flow for which the formula of Poiseuille holds:

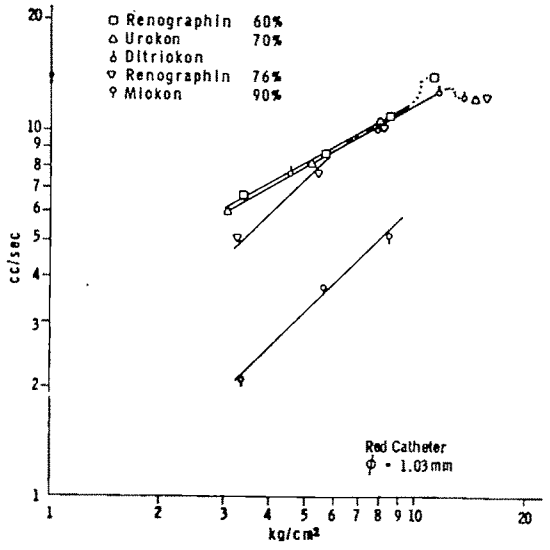
$$F = \frac{\pi \times P \times a^4}{8 \times \eta}$$

in which F = flow in volume per time, $P = p/l$, p = pressure, l = length, a = radius, and η = viscosity. Thus, the law of Poiseuille, which is only valid for "moderate" velocities, says that the volume of efflux per time varies directly with the pressure, and the fourth power of the radius, and inversely with the length of the tube and the viscosity.

Table II

DIAMETER IN MM.

	Red	Green	Yellow
Ödman[9]	1.15	1.3	1.5
Mercury method	1.10	—	1.57
Microtome method	1.03 ±0.04	1.12 ±0.04	1.54 ±0.05
Schick X-ray Company	—	1.14	1.57



GRAPH 1.

Two corrections of this formula should be considered: the Couette correction, and the kinetic energy correction.[1] Since the correction terms in this formula are not very large and since our measurements do not justify such accuracy, we have used the uncorrected Poiseuille's formula in the calculations which follow.

We have made a calculation of the expected outflow for Miokon 90% by means of Poiseuille's formula for a pressure of 1.9×10^6 newton/m.^{2} (4 kg./cm.^{2} on the meter dial or 19.4 kg./cm.^{2} inside the injection cylinder equaling 275 lb./in.^{2}) and we obtained for the red, green, and yellow catheter respectively 2.5 cc./sec., 3.3 cc./sec., and 11.9 cc./sec. when the measured outflow was 2.6 cc./sec., 3.2 cc./sec., and 11 cc./sec. This once more demonstrates that the flow rate for Miokon 90% follows Poiseuille's formula.

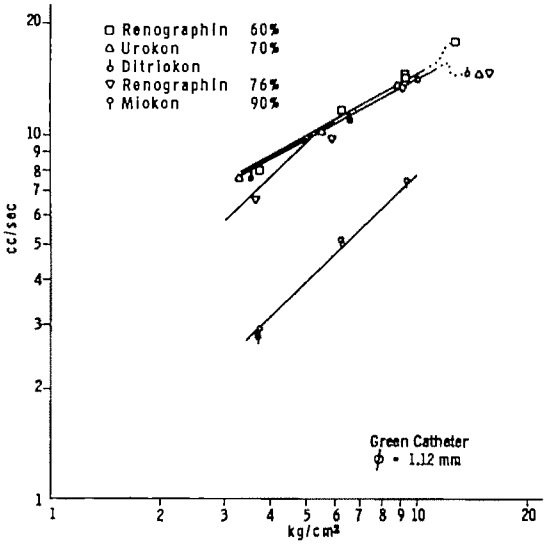
For the other media, a region must have been reached in which interlacing and constantly varying streams cross the tube, a region of so-called turbulent flow. In 1913 Blasius published a formula for turbulent flow[6,8,11] which can be written as:

$$F=\frac{\pi\times a^{2\,5/7}\times P^{4/7}}{c^{4/7}\times\rho^{3/7}\times\eta^{1/7}},$$

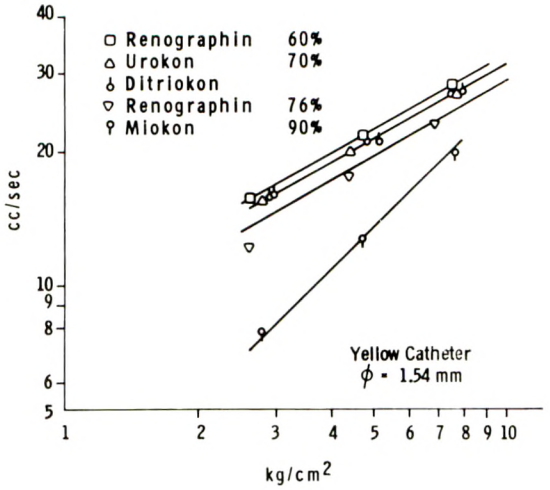
in which a = radius of the tube, η = viscosity, P = the pressure per length, c = 0.0664, and ρ = density. Thus, the outflow apparently would no longer be proportional to P but to $P^{4/7}$ In our Graphs, the slope of the lines other than for Miokon 90% and Renografin 76% is exactly 4/7. Here again we have calculated the expected flow for several sets of values; the measured flow rate was indeed in close agreement with these values. For instance, again for a pressure of 1.9×10^6 newton/m.^{2}, the calculated flow rates for Ditriokon with the red, green, and yellow catheters respectively were 6.7 cc./sec., 8.1 cc./sec., and 19.3 cc./sec.; the measured values were 7.0 cc./sec., 8.6 cc./sec., and 19 cc./sec.

As a further test of the validity of the two formulas, we have plotted in Graph 5 the flow rates at a constant pressure, namely 5 kg./cm.^{2}, obtained by interpolation against various catheter diameters (Table III).

The lines for Renografin 60%, Urokon 70%, and Ditriokon show a slope of approximately 2 5/7, whereas that for Miokon is 4 (both as predicted by the two formulas of Blasius and Poiseuille). As a matter of fact, the lines in Graph 4 for catheter No. 7 are all calculated. It was not possible to



GRAPH 2.



Graph 3.

draw in both the calculated and measured lines since they came exceedingly close. Therefore, we may well say that a description with Blasius' and Poiseuille's formula is satisfactory.

We can define resistance of a catheter as a factor relating pressure and flow rate. As long as we deal with a flow according to Blasius' *or* Poiseuille's formula, such relation is meaningful. Table IV shows the resistances for the different catheters (length 1 m.) and media. Pressures are again as read on the Gidlund pump. For the first three media, such resistance R would fit in a formula

$$F=\frac{P^{4/7}}{R} \quad (F \text{ in cc./sec.; } P \text{ in kg./cm.}^2 \text{ on the Gidlund pump});$$

and for the last medium these values would fit in a formula

$$F=\frac{P}{R}.$$

For instance, the flow rate for Ditriokon in catheter No. 7 having a length of 130 cm. at 7 kg./cm.^{2} would be

$$\frac{(7/1.3)^{4/7}}{0.14} \text{ cc./sec.} = \frac{2.62}{0.14} \text{ cc./sec.}$$
$$= 18.7 \text{ cc./sec.}$$

Likewise for Miokon 90% one obtains a value

$$\frac{5.4}{0.45} \text{ cc./sec.} = 12 \text{ cc./sec.}$$

Using these data, a table for flow rates can be constructed which is applicable to any catheter of the above diameter.

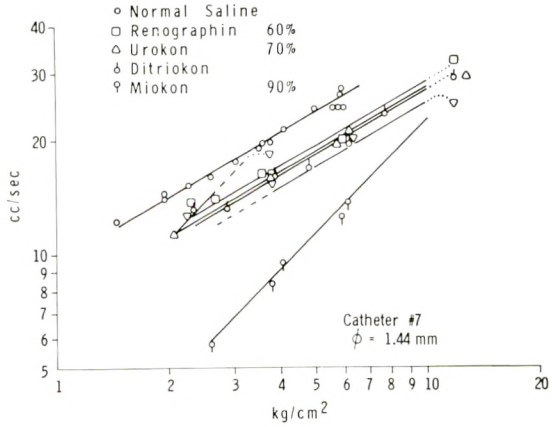
Reynolds derived a number below which laminar flow would take place and above which turbulent flow could start:

$$Re=\frac{.637\times\rho\times F}{a\times\eta}.$$

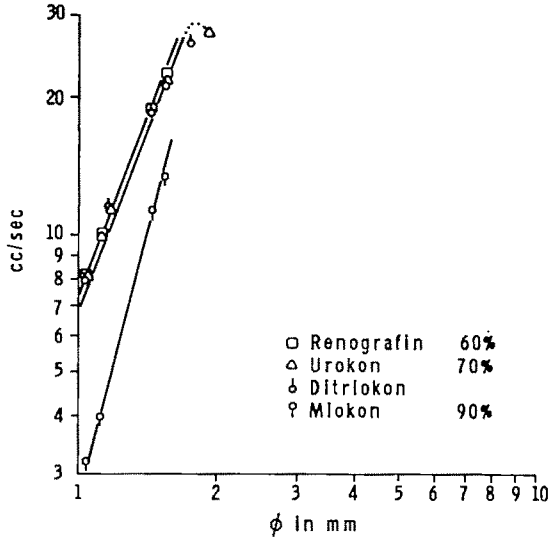
The critical value of this number is about 2,000.[6,8,11] For Miokon 90% with all of the pressures and catheters used, we are definitely under this value, whereas for Renografin 60%, Urokon 70%, Ditriokon, and saline, we are definitely over this value and also below a value of 100,000. Blasius' empirical formula now is valid up to about 100,000.[11] Renografin 76% is the only medium in our investigation which exhibits both types of flow. From Reynolds' number the pressure was calculated above which turbulent flow can exist:

$$P=\frac{8{,}000\times\eta^2}{\rho\times a^3}.$$

For Renografin 76% the following pressures are found beyond which laminar flow could turn into turbulent flow; for the red cathe-



Graph 4.



GRAPH 5.

ter at 7.2 kg./cm.², for the green catheter at 5.8 kg./cm.², for catheter No. 7 at 2.7 kg./cm.², and for the yellow catheter at 2.2 kg./cm.². The turbulence can be expected to maintain itself at pressures

$$P > \frac{11{,}800 \times \eta^2}{\rho \times a^3}.$$

Our measurements are in agreement with this.

In Graph 6 we have plotted the iodine in gm./sec. against the pressure using the yellow catheter.

If one considers the grams of iodine per second as the main factor for the opacity in the roentgenogram, assuming that the total amount is constant, it becomes clear that only for media in laminar flow the concentration of the iodine over the viscosity C/η is the criterion for the suitability of a contrast substance for injection; for turbulent flow this criterion would be the concentration of iodine over the density$^{3/7} \times$ viscosity$^{1/7}$

$$\frac{C}{\rho^{3/7} \times \eta^{1/7}}$$

assuming that the radius of the catheter and the pressure are the same in both cases. If the flow is turbulent and cannot be brought into a laminar behavior, a better injection will be obtained as the concentration of iodine increases provided that this change is not offset by a considerably greater change in viscosity and/or density. If, for instance, the concentration of iodine could be increased by a factor 1.5 even with a similar increase of 1.5 for both density and viscosity, this still would result in a more favorable injection. Table v shows the concentration of iodine (C) over the density$^{3/7} \times$ viscosity$^{1/7}$ in relative units for the different media as mentioned in the previous list.

The middle column in this table gives the rating for fluids in turbulent flow. The last column in this table gives the Reynolds' numbers for a pressure of 5 kg./cm.² and the yellow catheter ϕ 1.54 mm., length 1 meter. At this pressure and diameter, Miokon 90% is the only "laminar" medium.

To compare laminar flow (subscripts 2) with turbulent flow (subscripts 1), the following expression f could be used, derived

TABLE III

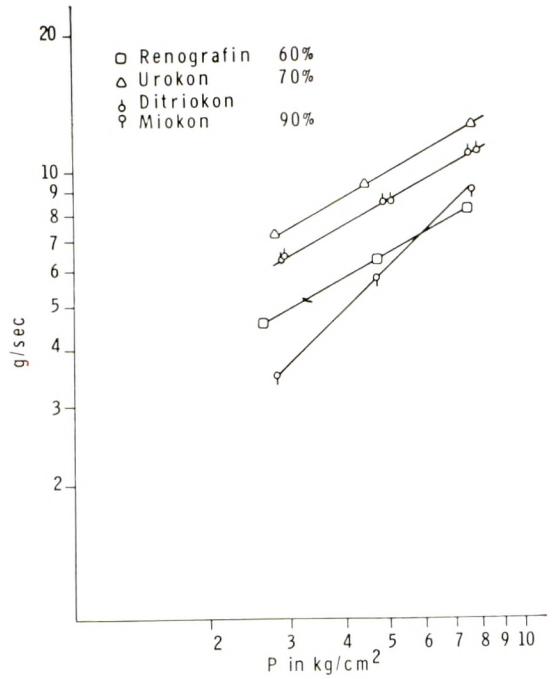
FLOW AT 5 kg./cm.² (344 lb./in.²)

Catheter	Diameter in mm.	Renografin 60% cc./sec.	Urokon 70% Ditriokon cc./sec.	Miokon 90% cc./sec.
Red	1.03	8.15	8.0	3.2
Green	1.12	10.2	9.9	4.0
No. 6	1.17	—	11.4	—
No. 7	1.44	18.9	18.5	11.4
Yellow	1.54	22.7	21.5	13.5
No. 8	1.73	—	26.5	—

TABLE IV

RESISTANCES FOR DIFFERENT CATHETERS (1 m. length)

	Red	Green	No. 7	Yellow
Ditriokon	0.32	0.25	0.14	0.12
Renografin 60%	0.31	0.25	0.14	0.11
Urokon 70%	0.32	0.25	0.14	0.12
Miokon 90%	1.55	1.24	0.45	0.37



Graph 6.

from Blasius' and Poiseuille's formulas:

$$f = 0.048 \times (Re_2)^{3/7} \times \frac{C_2}{\rho_2^{3/7} \times \eta_2^{1/7}} \times \frac{\rho_1^{3/7} \times \eta_1^{1/7}}{C_1},$$

in which Re_2 is Reynolds' number for medium 2

$$\left(Re = \frac{\rho a^3 P}{4\eta^2}\right),$$

the medium in laminar behavior, and

$$\frac{C}{\rho^{3/7} \times \eta^{1/7}},$$

the criterion given in the previous table. The rate of iodine output by medium 2 is the fraction f of the iodine output by medium 1. Therefore, if this expression f is greater than 1, laminar medium 2 has a higher output than turbulent medium 1.

Since Reynolds' number is directly as the radius cube and as the pressure, laminar flow will become more favorable when the diameter increases and when the pressure is larger. In Graphs 1 through 4, one can see this behavior since the line for Miokon 90% is closer to the other media for the larger bore than for the smaller bore and more so for the larger pressure than for the smaller pressure. This, of course, holds as long as Reynolds' number is under 2,000 since otherwise the fluid may leave the laminar region.

The first two factors of our expression f,

$$0.0483 \times (Re)^{3/7} = 1 \qquad \text{if } Re = 1{,}200$$

and

$$= 1.25 \qquad \text{if } Re = 2{,}000.$$

Therefore, if two media have the same criterion value

$$\left(\frac{C}{\rho^{3/7} \times \eta^{1/7}}\right),$$

and one has a Reynolds' number well over 2,000 and the second a Reynolds' number between 1,200, and 2,000, this last one will surpass the first one in performance. If the laminar flow takes place at a Reynolds' number of less than 1,200 the turbulent flow will always be more advantageous for two media with the same criterion value.

On the other hand, laminar flow may outperform turbulent flow even if our criterion

$$\left(\frac{C}{\rho^{3/7} \times \eta^{1/7}}\right)$$

has a lower value for the laminar medium; this will occur only when our criterion value for the laminar medium multiplied by $0.048 \times (Re)^{3/7}$ is larger than the criterion value for the medium in turbulence. Therefore, it appears that no medium in laminar behavior can be superior if its criterion value is less than 80% of that of a turbulent medium. For example, Miokon 90% should outperform Ditriokon in catheter No. 8 ($\phi = 1.73$ mm.) at a pressure of 8 kg./cm.^{2}; however, it will never surpass Urokon 70% since $0.8 \times 4.42 = 3.54$ which is larger than 3.40 (see Table v).

TABLE V

CONCENTRATION OF IODINE

Contrast Substance	$\frac{C}{\rho^{3/7} \times \eta^{1/7}}$	Diameter $\phi = 1.54$ mm. $P = 5$ kg./cm². Reynolds' No.
Urokon 70%	4.42	6,100
Ditriokon	3.78	4,900
Diodrast 70%	3.50	6,700
Renovist	3.46	4,100
Miokon 90%	3.40	825
Hypaque 50%	3.31	11,700
Renografin 76%	3.25	2,600
Miokon 50%	3.10	9,800
Renografin 60%	2.98	6,500

SUMMARY

Our data suggest that in most practical cases Blasius' law rather than Poiseuille's law should be applied to establish the expected flow rates of contrast substances injected through catheters. A formula is derived for the resistance of a catheter which can be applied similarly to the resistance as could be used in the law of Poiseuille. A criterion is given for the evaluation of a contrast material.

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Vol. 89, No. 2

THE USE OF RADIOIODINATED (I^{131}) IODIPAMIDE FOR CARDIOVASCULAR SCANNING*

By WILLIAM J. MacINTYRE, Ph.D., GODOFREDO GOMEZ CRESPO, M.D., *and* JAMES H. CHRISTIE, M.D.
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THE visualization of large vascular pools by the automatic scintillation scanner and its use in the differential diagnosis of pericardial effusions, vascular aneurysms, and mediastinal masses have been established by the work of Rejali *et al.*[3,14] In this technique, radioiodinated serum albumin in amounts up to 400 μc was injected intravenously in order to establish counting rates sufficiently high so that the deposition of radioactivity in the large vascular pools might be distinguished from the surrounding environment of lesser activity. Even with dosages in this range, the peak counting rates have rarely exceeded 1,200 counts per minute; and with selected scanning speeds of 10 inches per minute, extreme care must be exercised in accentuation methods[7] to accurately delineate the edge of the vascular pool.

This present investigation has been concerned with the establishment of a suitable radioactive scanning material that would exhibit reasonable stability in the vascular system during the scanning period but would be rapidly eliminated by the patient. In this way large doses could be utilized for high statistical counting accuracy while still maintaining a permissible whole body radiation exposure.

METHOD

With the patient positioned under the scintillation scanner, as shown in Figure 1, 300 to 750 μc of iodinated (I^{131}) serum albumin or 1 to 1.5 mc of iodinated (I^{131}) iodipamide* was injected intravenously. Scanning was started immediately from the sternal notch progressing toward the xiphoid. The collimators used in the study consisted of a 3 inch straight bore with a $\frac{1}{2}$ inch aperture and a 19 hole Picker X-Ray† experimental point focus collimator of 3 inch focal distance. A scan speed of 8 inches per minute was used throughout and dot-scans were obtained of the radioactivity distribution. The variation of counting rate with linear traverse across the body was recorded before scanning in order to obtain the settings for the cut-off levels[8] and for linear profile representation.[9]

Of the 28 patients studied, 11 vascular scans were performed with radioiodinated (I^{131}) iodipamide (one on each patient) and 21 vascular scans were obtained on 17 patients administered radioactive (I^{131}) albumin. For estimation of body dose and turnover, 50 μc of tagged iodipamide was injected intravenously in 8 patients and blood samples taken at 10 minutes, 70 min-

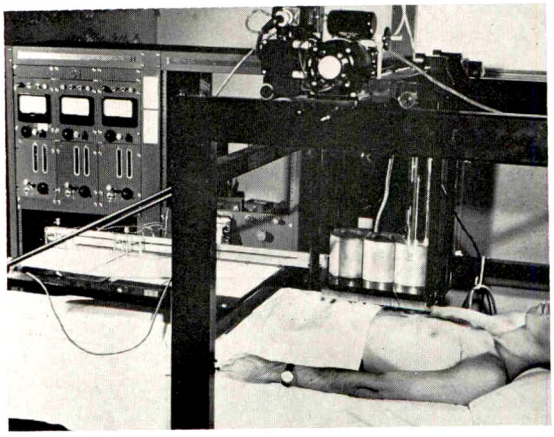


FIG. 1. Patient in position under scintillation scanner for cardiac pool visualization.

* Supplied by E. R. Squibb and Sons, New York, as Radio-Cholografin ® through the courtesy of Dr. Paul Numerof.
† Picker X-Ray Corporation, White Plains, New York.

* From the Radioisotope Laboratory, Highland View Hospital, Cleveland, Ohio, and the Departments of Radiology and Medicine, Western Reserve University, Cleveland, Ohio.
This investigation was supported in part by a grant from the National Institutes of Health, U.S.P.H.S. #C-4961 Rad.

utes, 6, 24, and 48 hours. In some cases, 24 and 48 hour collections were made of both urine and feces for estimation of metabolic turnover.

RESULTS

Since the most critical differentiation involves the delineation between the vascularity of the lung field and the large vascular pools of the heart, the effectiveness of cut-off settings is dependent upon the actual difference in counting rate observed over these areas. In Figure 2 a linear profile is shown as obtained by passing the counter over the heart at the level of the fourth intercostal space. On the left in this Figure, the plateau of average lung activity is shown at about 40 per cent of the peak count over the heart, thus cut-off levels could be selected at 45 and 55 per cent to isolate the heart contour.

While the factors of geometric configuration, proximity of the heart to chest wall, size of heart, and dilution of the injected material by the circulating blood will all be variable with the patient, peak counting rates for the ½ inch straight bore collimator have averaged about 2,900 counts per minute per millicurie of either material. This is shown in detail in Table 1. With a linear profile obtained at a speed of 1 inch per minute and a rate meter time constant of 5 seconds, a standard error of from 5 to 10 per cent can be expected at these typical counting rates. These parameters are ade-

TABLE I

PEAK COUNTING RATES OVER PRECORDIUM

Iodinated (I^{131}) Albumin		Iodinated (I^{131}) Iodipamide	
Patient	c/m per microcurie	Patient	c/m per microcurie
J. B.	1.9	J. B.	3.6
G. B.	5.0	G. N.	2.8
G. B.	3.6	F. S.	2.6
G. B.	2.2	J. S.	2.6
B. B.	2.7	J. F.	3.0
C. C.	3.6	L. B.	3.2
M. K.	2.4	G. C.	3.4
M. M.	2.4	A. P.	3.1
M. S.	2.5	H. P.	3.2
A. S.	3.3	E. B.	3.1
G. S.	3.0	W. S.	2.0
G. S.	3.1		
G. S.	2.5		
L. S.	2.0		
C. W.	1.6		
C. W.	1.8		
N. W.	3.0		
P. F.	2.4		
S. W.	4.6		
T. M.	4.8		
Average with standard deviation	2.9±1.0		3.0±0.45

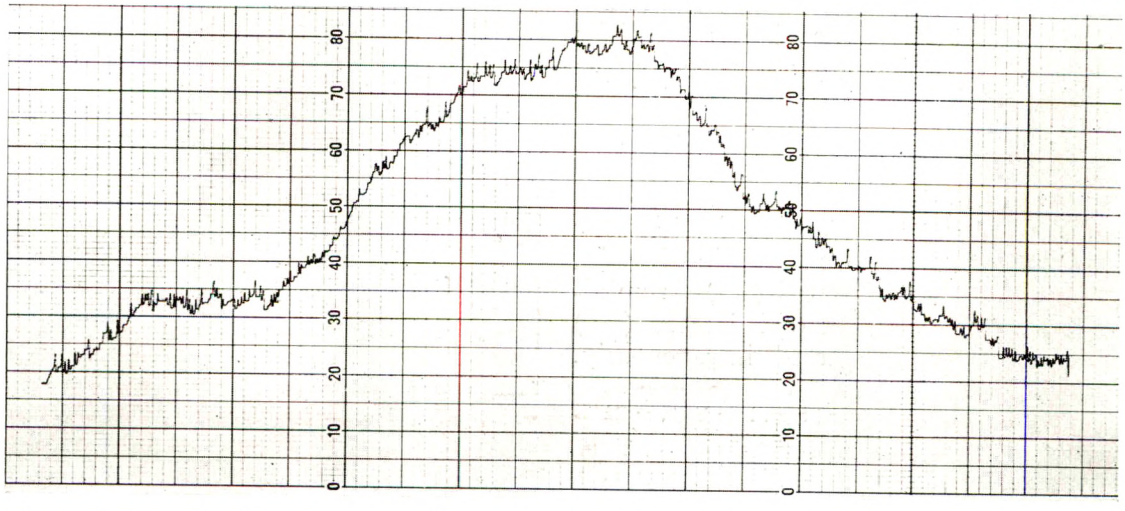


FIG. 2. Linear profile of counting rate variation as detector is passed over the heart at the level of the fourth intercostal space. The "plateau" on the left represents the right lung field activity.

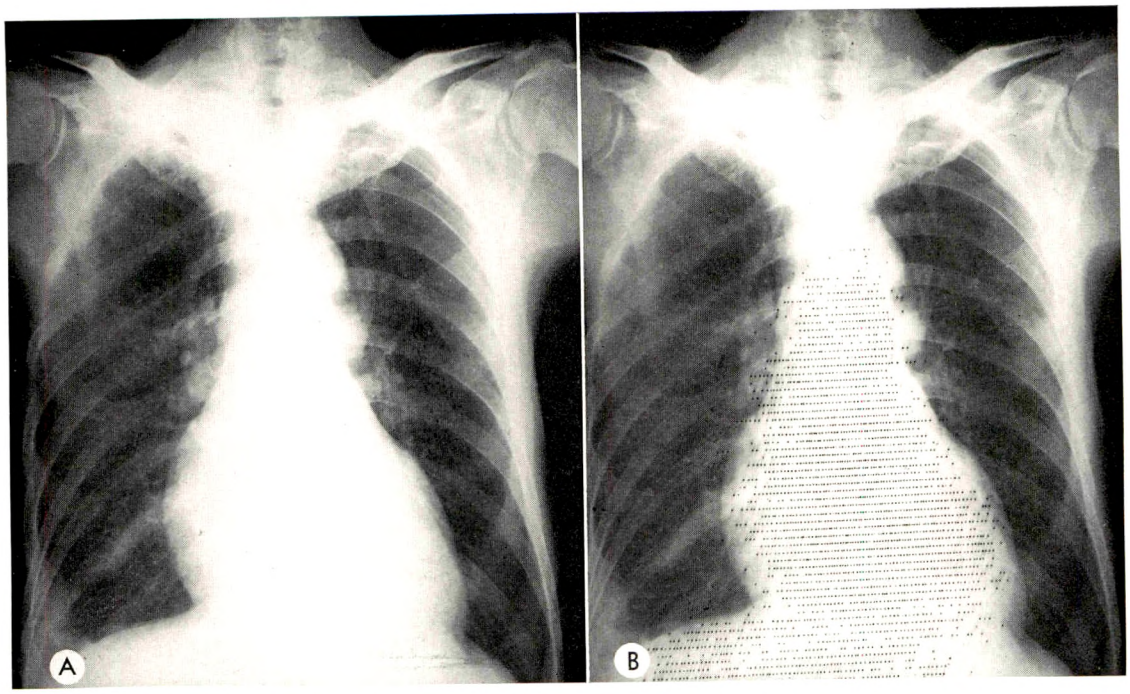


Fig. 3. (*A* and *B*) Normal heart scanned with 1.5 mc of radioiodipamide. Note appearance of the superior margin of the liver.

quate to delineate the heart and lungs as long as there is a counting rate differential of at least 20 per cent between these organs. Where the difference in counting rate is less than 20 per cent, slower linear scanning times with longer time constants will be required in order to determine the cut-off level.

In Figure 3, a scan of the normal heart obtained with 1.5 mc of radioiodinated (I^{131}) iodipamide is shown. Figure 3*B* shows the coincidence of the vascular area with the cardiac silhouette on the conventional roentgenogram. Figure 4, *A* and *B* shows a similar comparison in a patient with a pleural effusion. Note the complete loss of heart outline on the posteroanterior roentgenogram that can be completelydelineated by the radioisotope method.

Figure 5*A* shows an enlarged cardiac silhouette which clinically either represented a greatly enlarged heart or a large pericardial effusion. A scan (Fig. 5*B*) following the injection of 1.5 mc of I^{131} iodipamide shows the vascular area to fill almost the entire heart outline. The discrepancy at the apical area, due to motion and geometric configuration, is often seen in enlarged hearts and makes adequate visualization of this region difficult.

Figure 6*A* shows an abnormal cardiac silhouette with great prominence in the region of the left pulmonary artery. To rule out lymphadenopathy, a cardioscan was deemed advisable. The scan (Fig. 6*B*) following the injection of 1.5 mc of I^{131} iodipamide demonstrates this region to be vascular. (Note again the left ventricular discrepancy.)

In Figure 7, *A* and *B* an abdominal scan of a pulsating midline mass was obtained following the administration of 1.0 mc of I^{131} iodipamide. Clinically and roentgenographically this was characteristic of an abdominal aneurysm. The scan has defined this mass as an area of decreased activity, 30 per cent less than its surrounding environment. This decrease suggests that the aneurysm contained clotted blood and that the pulsations were transmitted. Because of the release of this material into the intestine, the surrounding high counting rate

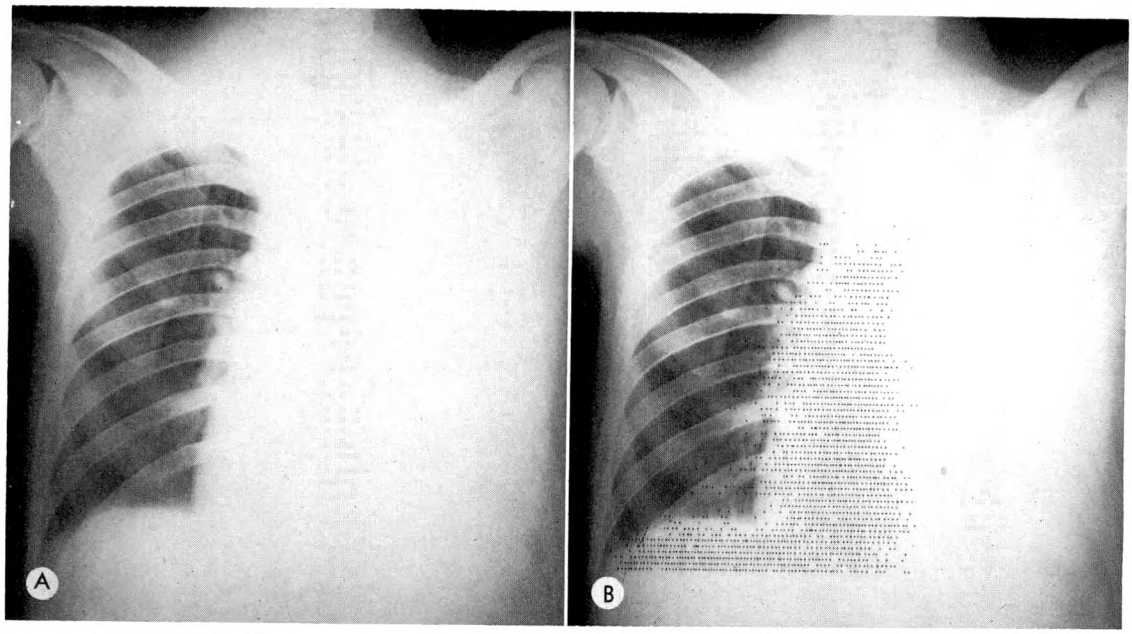


FIG. 4. (*A*) Chest roentgenogram and (*B*) cardioscan of patient with pleural effusion. Note displacement of heart to the right and flattening of the left border. Six-foot recumbent chest roentgenograms are obtained with the patient breathing quietly to reproduce normal scanning conditions.

is undoubtedly a reflection of both abdominal vascularity and radioactivity in the bowel.

DOSAGE CALCULATIONS

The disappearance of the tagged iodipamide in the circulating blood of 10 patients is shown in detail in Table 11 and in graphic form in Figure 8. The disappearance does not follow a single exponential decay, but instead exhibits a half life of 160 minutes initially which increases to a half life of 12 hours or more by the end of the first day. Integrating this curve over the first 24 hours has indicated an average life of approximately 9 hours.

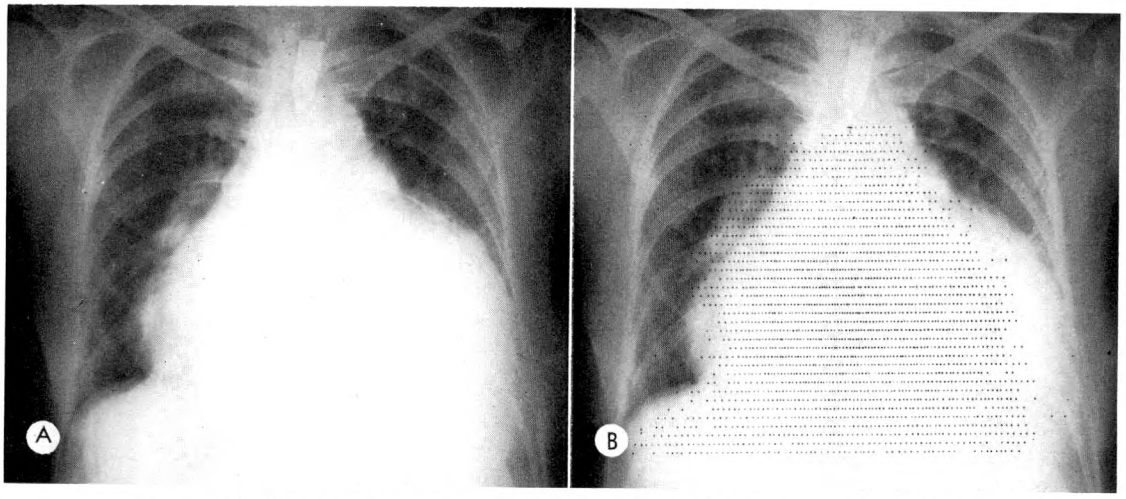


FIG. 5 (*A*) Chest roentgenogram and (*B*) cardioscan showing an enlarged heart. Note discrepancy on the left heart edge.

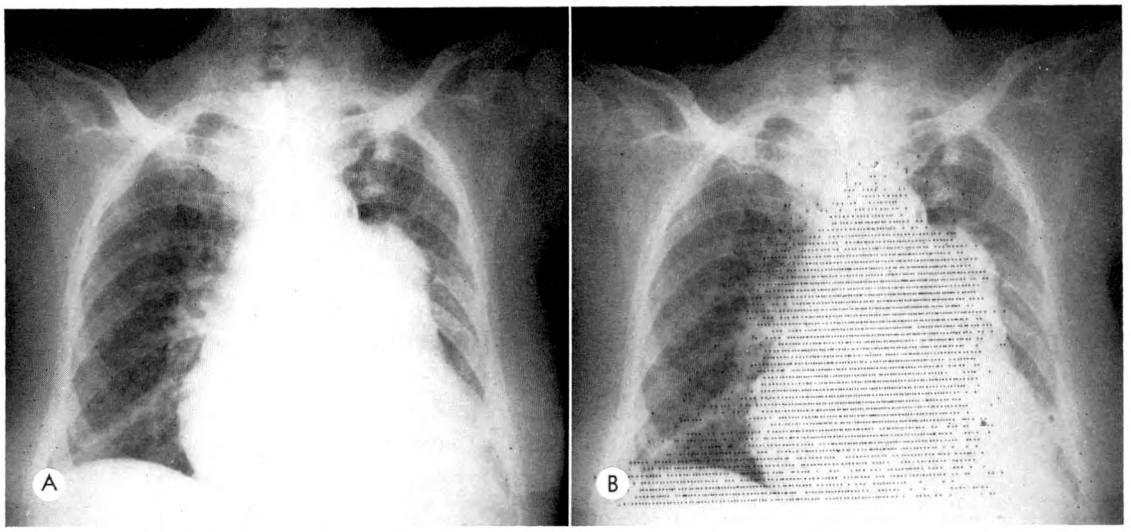


Fig. 6. (*A*) Chest roentgenogram showing an enlarged cardiac silhouette with abnormal widening of the base. (*B*) Prominence at the base identified as vascular by cardioscanning.

Comparing this value to the half life of radioiodinated (I^{131}) serum albumin of 6 days (201 hours average life)[15] predicts that less than one-twentieth of the total dose would be caused by the radioiodipamide as compared to the radioalbumin.

The dose for tagged albumin is dependent upon the volume of dilution assumed. Because of the closeness of blood vessel spacing, whole body dilution has usually been

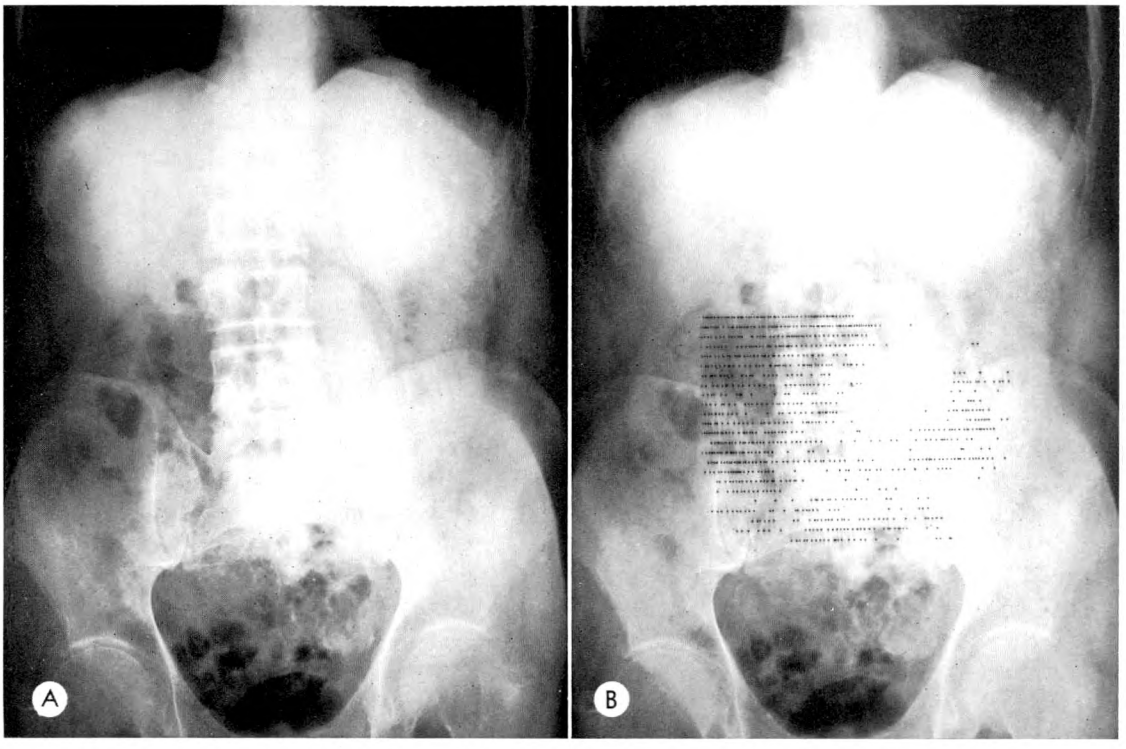


Fig. 7. (*A*) Abdominal mass is shown to be region of decreased activity (*B*) by scanning.

TABLE II

PER CENT OF RADIOACTIVITY REMAINING IN CIRCULATING BLOOD

Patient	Time of Blood Sample Withdrawal		
	70 min.	6 hr.	24 hr.
L. B.	74.0	39.0	18.5
E. M.	64.5	27.4	5.6
J. F.	71.8	33.3	7.1
J. S.	85.5	37.6	12.4
F. S.	81.5	64.2	
G. N	85.5	58.0	23.6
C. C.	68.0		
H. J.	81.0		
A. S.	73.0		
W. S.	76.0	44.9	12.0
Average with standard deviation	76.0±7.1	43.5±13.5	13.2±6.8

assumed.[15] With this assumption, 400 μc of radioiodinated (I^{131}) serum albumin would give an average absorbed dose of approximately 460 millirads for the first week or about 760 millirads total. On a similar basis 1.5 mc of radioiodinated (I^{131}) iodipamide would result in approximately 127 millirads total.[6]

In respect to absorbed dose in specific concentrated sites, the liver, intestine, and gonads must all be considered. Initially, the measurements over the liver may show an increase up to 40 per cent over the equilibrium level. This concentration, however, is temporary and would be responsible for only a slight increase in total absorbed dose.

Since up to 75 per cent of this material is eliminated by the bowel, the specific concentration in feces will be important. For purpose of calculation, it is assumed that an average of 210 gm. of feces is eliminated per day[4] and an average of 62 per cent of the dose is recovered from the feces in 48 hours.[10] Thus, if 31 per cent of an administered dose of iodipamide could be removed in 24 hours, the specific concentration in feces would approximate 2.2 μc per gm. from a 1.5 mc dose. Using the analysis of Loevinger *et al.*[6] for a beta particle slab of infinite thickness, the dose on the surface of the feces would be 435 millirads per hour. At a distance of 0.5 mm. from the fecal mass, the dose rate would be approximately 44 millirads per hour, and at 1 mm. this is reduced to less than 6 millirads per hour.

The contribution to the wall of the intestine for gamma radiation is, of course, determined by the geometric distribution assumed. It is doubtful whether maximum concentration would ever be greater than a 3.7 cm. radius sphere (volume 211 $cm.^3$). Assuming this, the dose on the surface of the sphere would be approximately 113 millirads per hour. One would expect that generally the feces would be contained in a cylinder of diameter 2 cm. or less, in which case the surface dose rate would be no more than 30 millirads per hour.

The dose absorbed by the gonads can be no more than an estimate. If it may be assumed that the ovaries could be as close

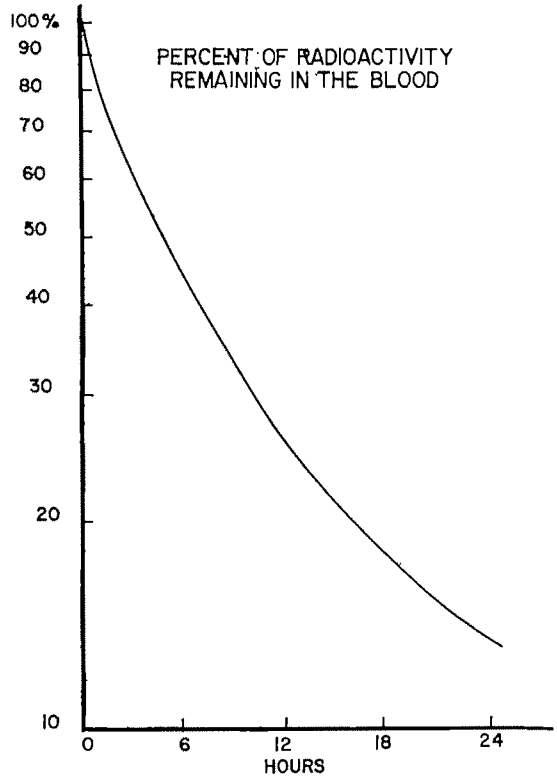


FIG. 8. Percentage of intravenously injected I^{131} iodipamide remaining in the blood as a function of time.

as 3.7 cm. to the wall of the greatest accumulated mass (the 3.7 cm. sphere representing 211 $cm.^3$ of feces in the rectum), the dose rate would amount to 10.2 millirads per hour. During the time when the feces are in the sigmoid colon, a dose rate of 2.7 millirads per hour may be received by the left ovary which could be as close as 1 cm. As pointed out by Comas and Brucer,[1] the total gonadal dose from passage of I^{131} through the kidney would amount to no more than 5 millirads for the estimated 0.3 mc that may be eliminated by renal excretion.

DISCUSSION

The loss of radioiodipamide from the circulating blood during the first hour has averaged 24 per cent as compared to an average loss of 7.6 per cent with iodinated (I^{131}) serum albumin.[11] This loss has been compensated for in most cases by scanning from the sternal notch to the xiphoid. By this method the detector is moving from a lesser to a greater vascular pool so that the counting rate decrease due to blood concentration loss is partially balanced by the increase in pool volume. Such compensation, however, cannot always be realized if the clearance of this material by the liver is rapid. It is recommended that a 10 μc tracer dose of radioiodipamide be administered with 10 minute and 70 minute samples taken before scanning is initiated. If the loss is greater than 30 per cent, a faster scanning speed must be selected.

The removal time will vary considerably with the individual patient. Previous investigations[10] have determined that half of this material has been removed from the circulating blood in an average of 112 minutes. While our average removal at this time is close to this value (65 per cent in 112 minutes) in both groups of patients, the variation is large.

The elimination of radioiodipamide from the intestine may vary considerably from one patient to another. While the dose rate is not excessive on an hourly basis, it is obvious that long exposures are possible and should be reduced by suitable catharsis.

With respect to the method itself, it is felt that some attention should be paid to the technique shown by the profile representation of Figure 2. While radioscanning is primarily one of visualization of the entire area, it is possible that suitable profiles juxtaposed on the posteroanterior roentgenograms may be equally useful. It should be emphasized that successful cardioscanning depends on adequate differentiation between the lung activity and the cardiovascular pool. It follows, therefore, that if the lung plateau is not seen on the profile, both the profile and the dotscan representations will be ill-defined.

While our present concern is with the use of radioiodipamide for studies involving 1 hour, success in this area indicates an even greater usefulness in general circulatory tests requiring the conventional 10 minute period. In our laboratory we have utilized this material for peripheral vascular investigations[2] and its use for cardiac output measurements has been reported elsewhere.[13] The choice of this material or any other rapidly clearing substance[5,12] must necessarily be a compromise between stability during the time of measurement and the desire to lower radiation exposure.

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CALCIFIC PULMONIC STENOSIS*

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CALCIFIC pulmonic stenosis is a rare entity, and one which has not been studied in detail. The following case is the first one to our knowledge in which the diagnosis was made on the basis of conventional roentgenologic study; supporting data were obtained from cardiac catheterization and angiocardiography; surgery confirmed the diagnosis and was curative; histopathologic studies of the excised valve were performed; and re-study 2 years after surgery demonstrated the disappearance of the right ventricular hypertension.

REPORT OF A CASE

M.W., a 40 year old male laborer, was seen at the Stanford University Outpatient Department in November, 1958, with a history of increasing exertional dyspnea of several months' duration. In 1941, a pre-induction physical examination revealed a heart murmur, and he was refused admission to the Armed Forces. His only prior symptom had been mild exertional dyspnea. He experienced no change in symptoms until May, 1958, when slight ankle edema, paroxysmal nocturnal dyspnea, nocturia, and a gradual increase in exertional dyspnea developed and caused him to leave his job in an onion factory in September, 1958. There was no history of rheumatic fever, hypertension, or angina pectoris. The patient had never been cyanotic.

Physical Examination. The patient was a well developed, well nourished, ruddy-faced male who was slightly dyspneic. The blood pressure was 130/100. The pulse was 90 and regular, and equal in the upper and lower extremities. Respiratory rate was 24. A prominent A wave was noted in the external jugular vein. There was venous distention in the neck up to the angle of the mandible with the patient recumbent at an angle of 45 degrees. The carotid pulsations were prominent. The lungs were clear.

The heart was enlarged 1 cm. to the left of the mid-clavicular line, and a right ventricular heave was present. A rough systolic murmur was noted at the left second intercostal space, but the pulmonic second sound was not identified. An early and a late diastolic sound were heard along the left sternal border and over the precordium. The liver was enlarged three finger breadths below the right costal margin. There was no evidence of ascites, ankle edema, clubbing, or cyanosis.

Laboratory Data. The hemoglobin was 16.8 gm. per 100 ml., the hematocrit 53 per cent. The arm-to-tongue circulation time with decholin was 29 seconds. Venous pressure in the left antecubital vein at the level of the left atrium was 12.2 cm. saline.

An electrocardiogram showed right ventricular hypertrophy and abnormal P waves suggestive of right atrial hypertrophy. Phonocardiograms confirmed the presence of a systolic murmur in the pulmonic area. A protodiastolic sound was also recorded, as were loud presystolic atrial sounds and a giant A wave.

Roentgenologic Studies. Fluoroscopic and roentgenographic examinations of the chest were performed (Fig. 1, *A–D*). The right atrial border was prominent. The right ventricle appeared somewhat enlarged, and there was gross dilatation of the main pulmonary artery which pulsated vigorously. The hilar and peripheral pulmonary arteries were at the low normal limit of size in contrast to the striking bulge of the main pulmonary artery. There was no evidence of left atrial enlargement. Fluoroscopy and cinefluorography revealed pulmonic valve calcification, best seen in the right anterior oblique and in the left lateral projection, presenting anteriorly and somewhat higher than aortic valve calcification (Fig. 2–4, inclusive). There did not appear to be significant movement of the valve cusps in relation to each other; instead, the cal-

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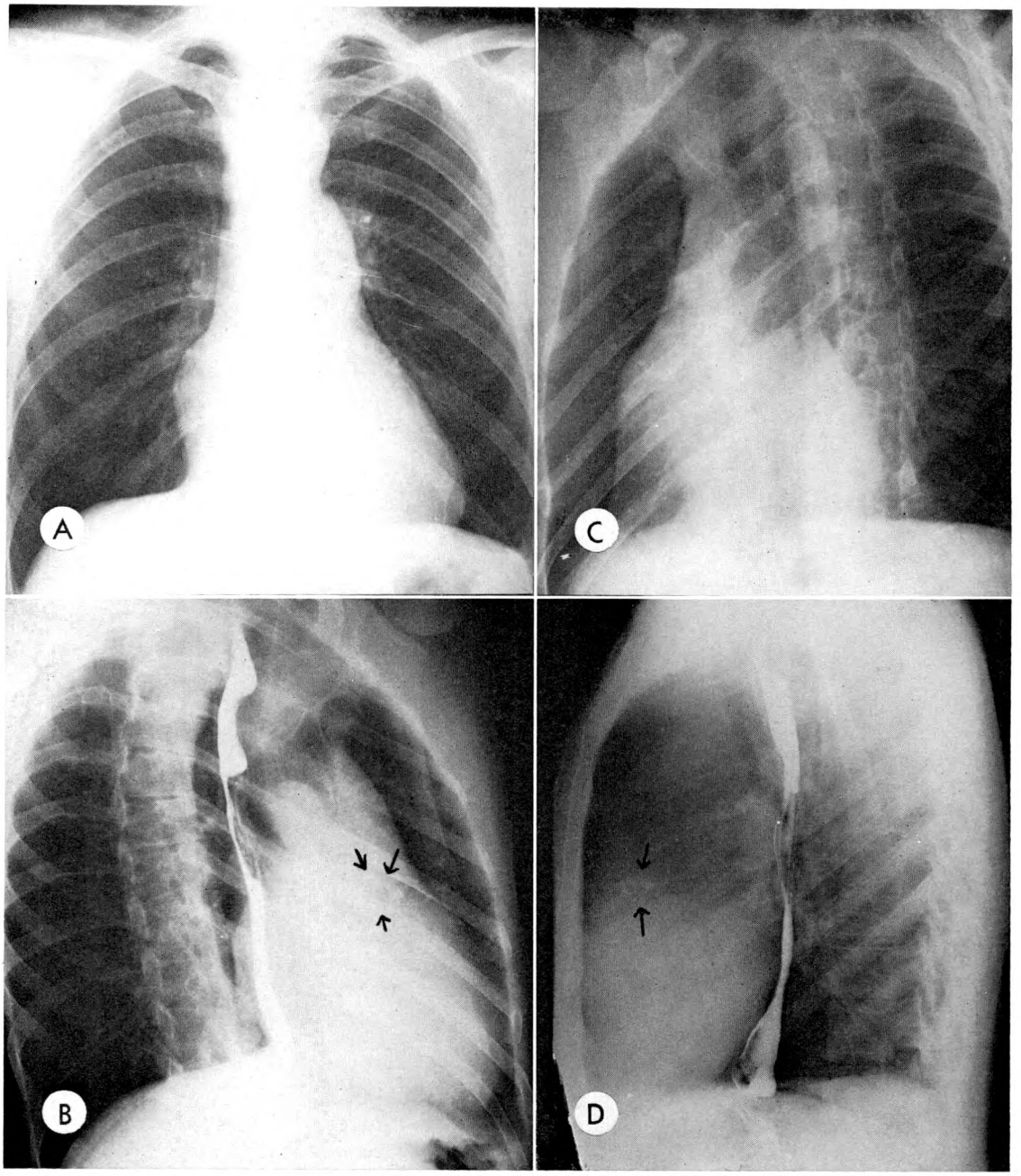


FIG. 1. Calcific pulmonic stenosis. (*A*) Posteroanterior view. The heart is somewhat enlarged with prominence of the right atrial border and the pulmonary artery segment. The pulmonary vascularity is in the low normal range. (*B*) Right anterior oblique view. The right atrial border extends posterior to the barium filled esophagus. No evidence of significant displacement of the barium filled esophagus to indicate left atrial enlargement is seen. The right ventricle appears somewhat enlarged. The calcification in the region of the pulmonary artery, anteriorly placed and at the valve level, is indicated by arrows. (*C*) Left anterior oblique projection. The calcification is not well delineated. The left ventricular border is displaced posteriorly and the right cardiac chambers are of moderate prominence. (*D*) Left lateral projection. There is filling in of the retrocardiac space by the prominent right ventricle and the enlarged pulmonary artery. The valve calcification is clearly demarcated and is in a significantly more anterior position than would be expected in aortic valve calcification.

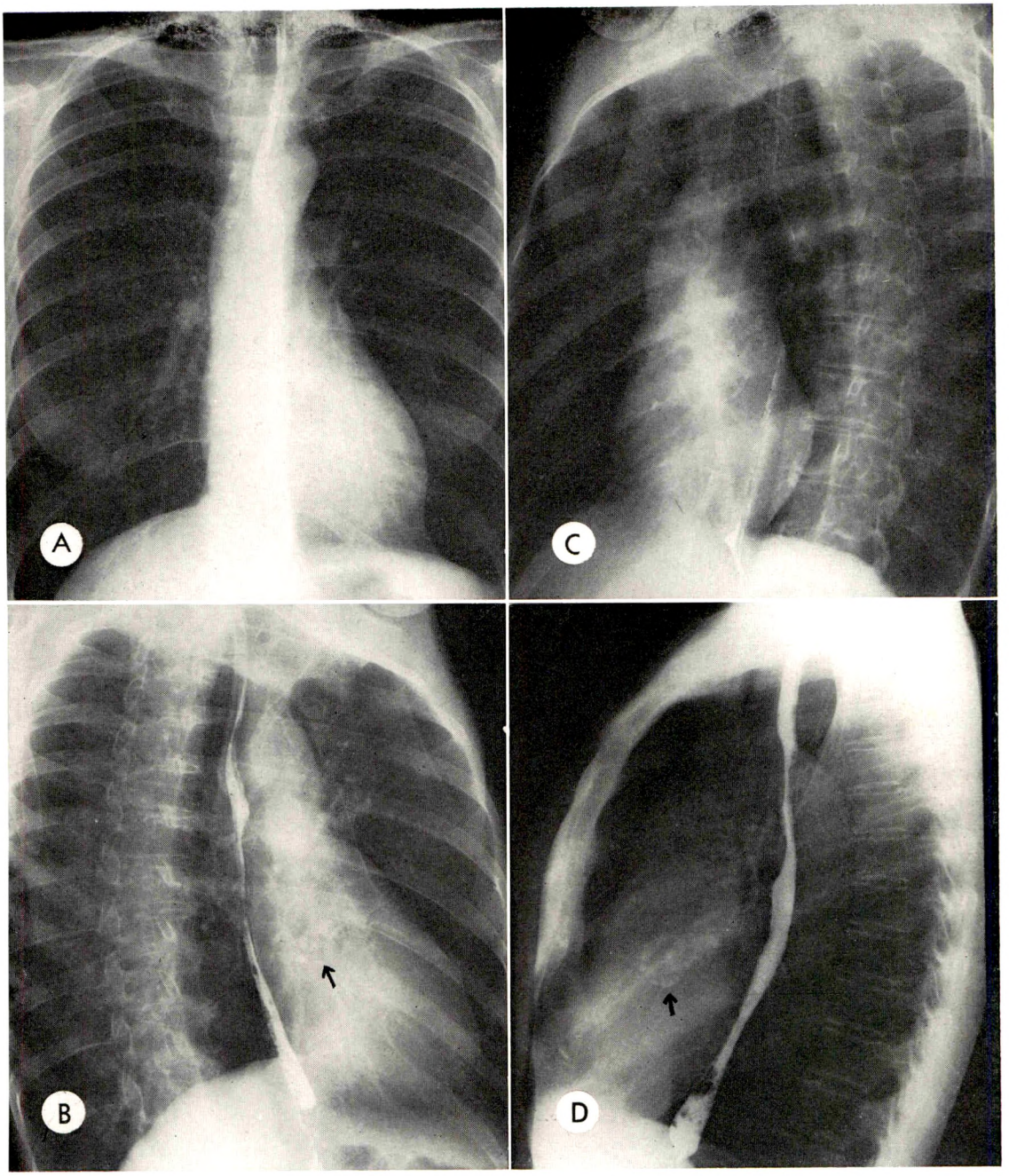


Fig. 2. Calcific aortic stenosis. (*A*) Posteroanterior view. There is no significant cardiac enlargement. The aortic knob is normally prominent. (*B*) Right anterior oblique projection. The valve calcification is clearly seen (arrow). It is somewhat more posterior in position and slightly lower as well. (*C*) Left anterior oblique projection. The calcification is poorly defined. The ascending aorta appears somewhat prominent. The left ventricle is not grossly dilated but is somewhat more prominent than normal. (*D*) Left lateral projection. The aortic valve calcification can now be clearly distinguished from that of the pulmonic valve by its relatively posterior position. Note that it is relatively anterior in position as compared to mitral valve calcification.

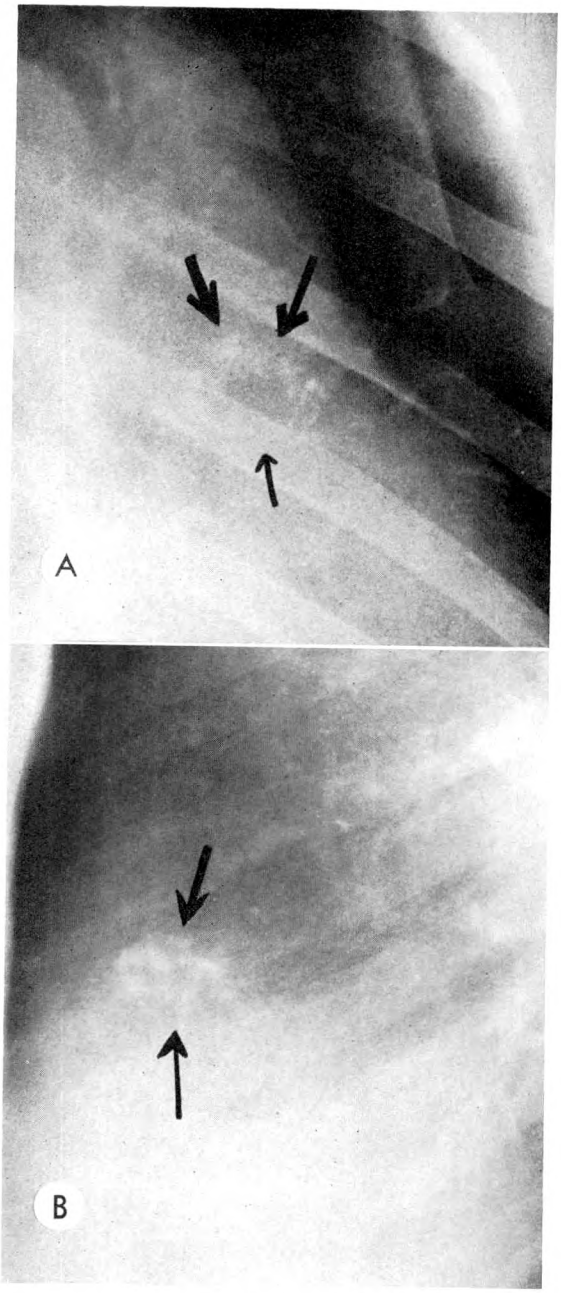


FIG. 3. Calcific pulmonic stenosis. Enlarged view of the calcified valve. (*A*) Right anterior oblique projection. (*B*) Lateral projection.

cifications moved caudad with systole and cephalad with diastole.

Cardiac Catheterization. The mean right atrial pressure was 13 mm. of Hg, the right ventricular pressure 193/20, and the brachial artery pressure 128/81 (Table 1). The pulmonary artery could not be entered. Oxygen samples demonstrated no evidence of left-to-right or right-to-left shunt. The cardiac output, calculated by the Fick principle, was 2.2 liters per minute, and the cardiac index 1.3 liters per minute/m^2. Spot roentgenograms taken at cardiac catheterization showed that the catheter tip in the outflow tract of the right ventricle was immediately ad-

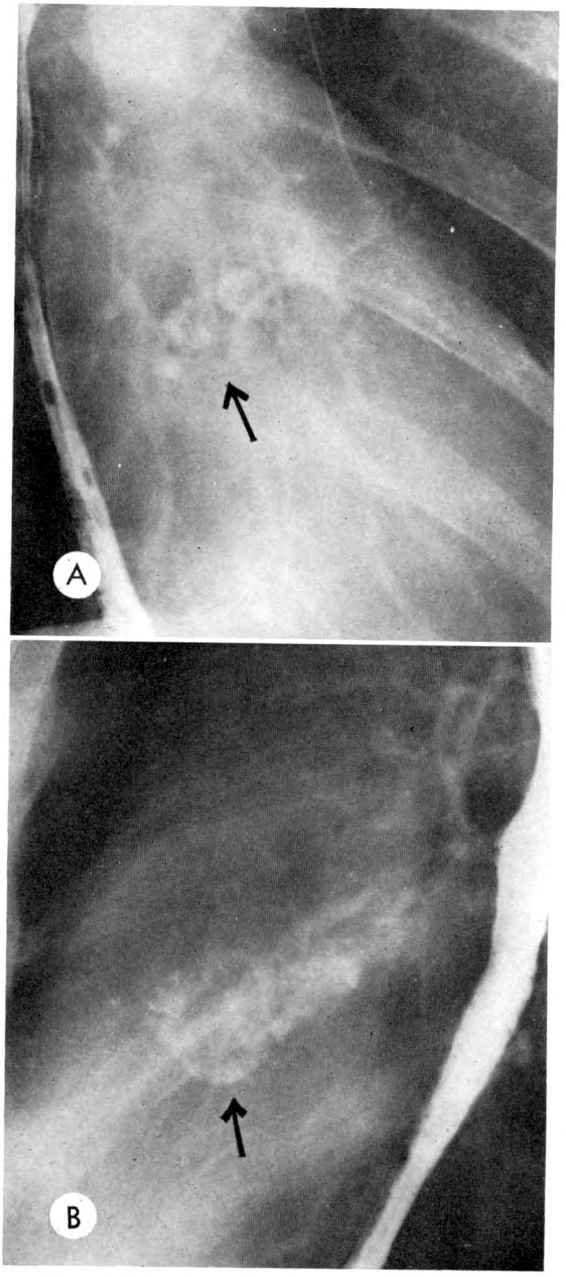


FIG. 4. Calcific aortic stenosis. Enlarged view of the calcified valve. (*A*) Right anterior oblique projection. (*B*) Lateral projection.

Table I

CARDIAC CATHETERIZATION DATA

	Pre-operative Pressures	Pressures 2 Years after Surgery
Right Atrium	13 mean	6 mean
Right Ventricle (Mid)		39/4
Right Ventricle (High)	193/20	28/4
Pulmonary Artery		23/8
Brachial Artery	128/81	135/81

jacent to the pulmonary valve calcification (Fig. 5, *A* and *B*).

Angiocardiography. Biplane angiocardiographic studies were performed with the catheter in the right ventricle (Fig. 6, *A–C* and *D–F*). Forty-five cubic centimeters of 90 per cent hypaque were injected under pressure. The right ventricular cavity was not grossly dilated, but there were marked thickening and trabeculation of the right ventricular wall. Gross hypertrophy of the crista supraventricularis, protruding into the posterior aspect of the infundibulum of the right ventricle, was visible. The pulmonic valve cusps were thick and immobile, and the size of the valve orifice was about 8 mm. Beyond the valve, aneurysmal poststenotic dilatation of the main pulmonary artery and the proximal portions of the right and left main branches was apparent. Passage of the contrast medium from the right ventricle into the pulmonary artery was strikingly delayed. No evidence of right-to-left shunt or of any left cardiac abnormalities was detected. The diagnosis of calcific pulmonic stenosis was made and the patient was scheduled for subsequent surgery.

Surgical Procedure. On April 9, 1959, a pulmonary valvotomy was performed, utilizing extracorporeal circulation. The pulmonary artery was opened through a longitudinal incision and a densely calcified bicuspid valve was visualized. This was partially excised. The major portion of the calcification appeared to occupy the ventricular aspect of the valve. The patient's postoperative course was uncomplicated. He was discharged from the hospital 12 days after surgey without maintenance digitalis. Chest roentgenograms following surgery showed in the lateral projection that the calcific densities noted in the region of the pulmonary valve were now spread apart by comparison with the preoperative studies.

Pathologic Findings. The specimen included two irregular fragments of dense white fibrous tissue, each bearing multiple irregular yellow verrucous masses of calcific density which covered about one-third of the surface. Histologic examination revealed that the section con-

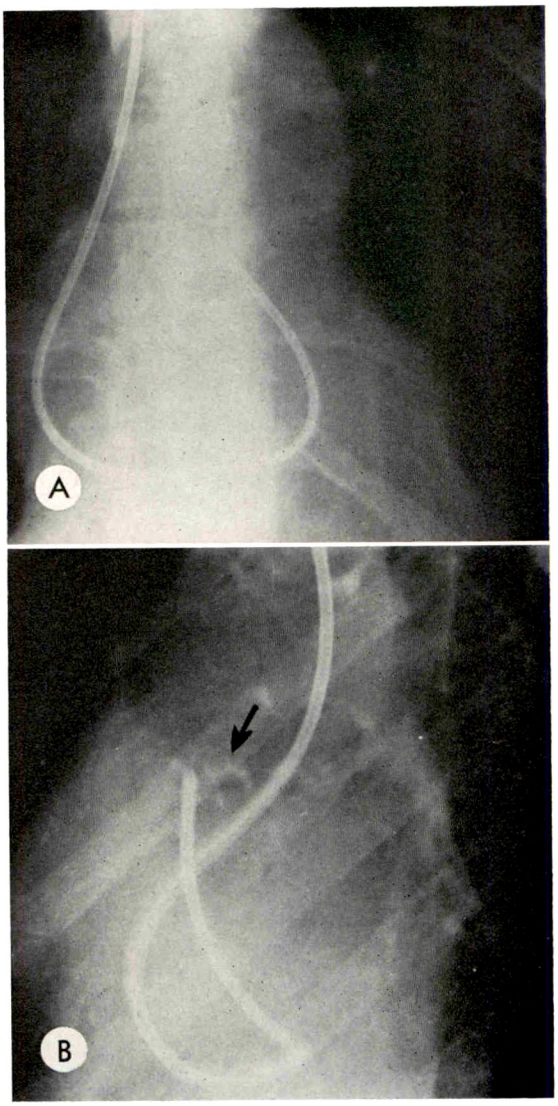


Fig. 5. Calcific pulmonic stenosis. (*A*) Posteroanterior and (*B*) left anterior oblique roentgenograms obtained during cardiac catheterization demonstrate the catheter tip in the outflow tract of the right ventricle in the immediate subvalvular position. It was impossible to pass the catheter through the valve into the pulmonary artery. The right ventricular pressure was 193/20.

sisted of acellular, hyaline fibrous tissue, surrounding multiple irregular masses of pale basophilic material, typical of calcium deposits. No cellular reaction was seen about the deposits, although elsewhere there were a few zones of loose fibroblastic tissue with small numbers of lymphocytes and macrophages. Small vessels were visible within the valve. Thus, the pathologic diagnosis of pulmonic stenosis, fibrosis and calcification, presumably associated with old endocarditis, was made.

Course. The patient was followed at intervals in the Outpatient Department and returned for cardiac catheterization in May, 1961, 2 years after surgery (Table 1). Right ventricular hypertension had disappeared, and there was no significant gradient at the pulmonic valve. A mild degree of infundibular stenosis, presum-

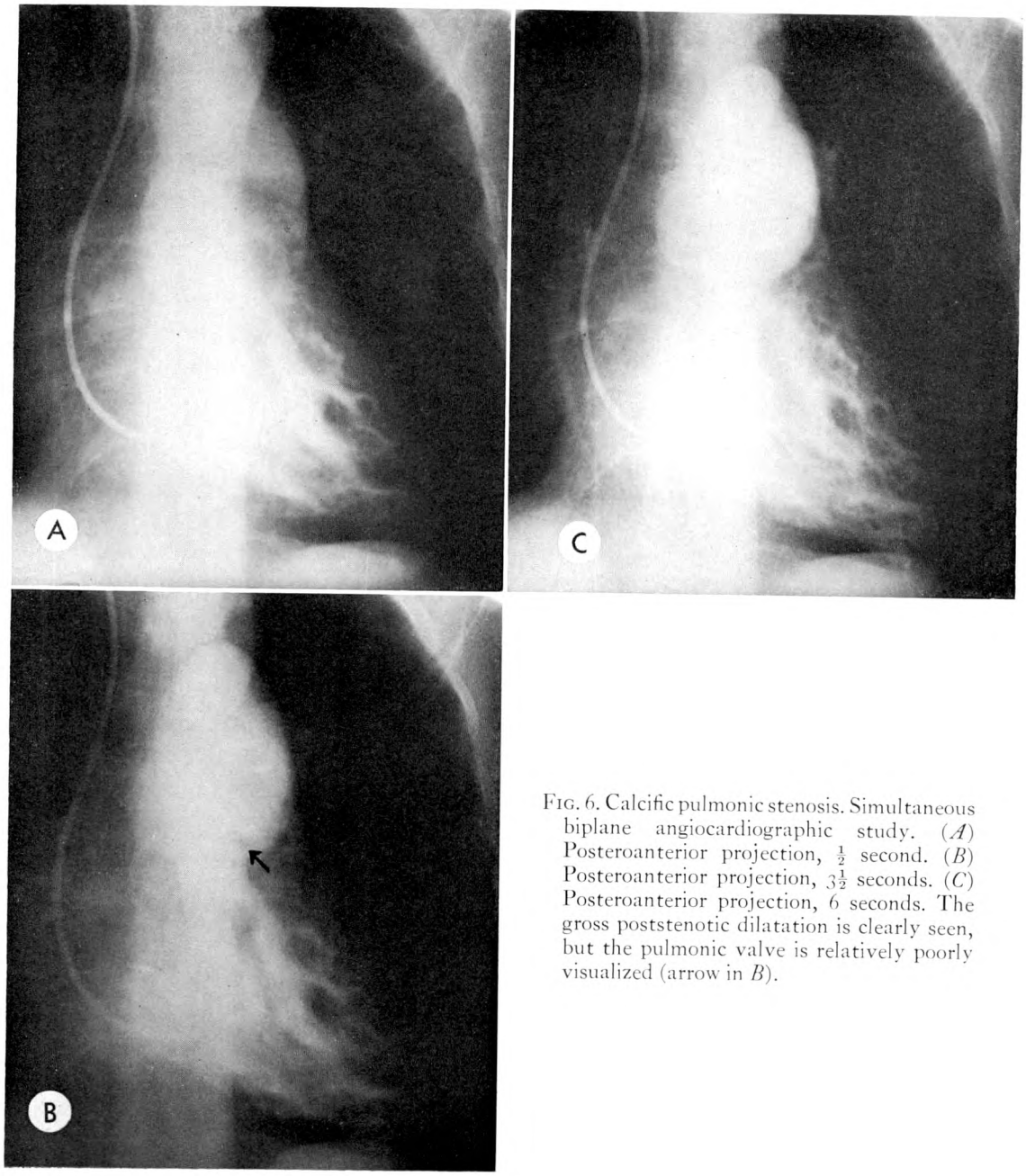


FIG. 6. Calcific pulmonic stenosis. Simultaneous biplane angiocardiographic study. (*A*) Posteroanterior projection, $\frac{1}{2}$ second. (*B*) Posteroanterior projection, $3\frac{1}{2}$ seconds. (*C*) Posteroanterior projection, 6 seconds. The gross poststenotic dilatation is clearly seen, but the pulmonic valve is relatively poorly visualized (arrow in *B*).

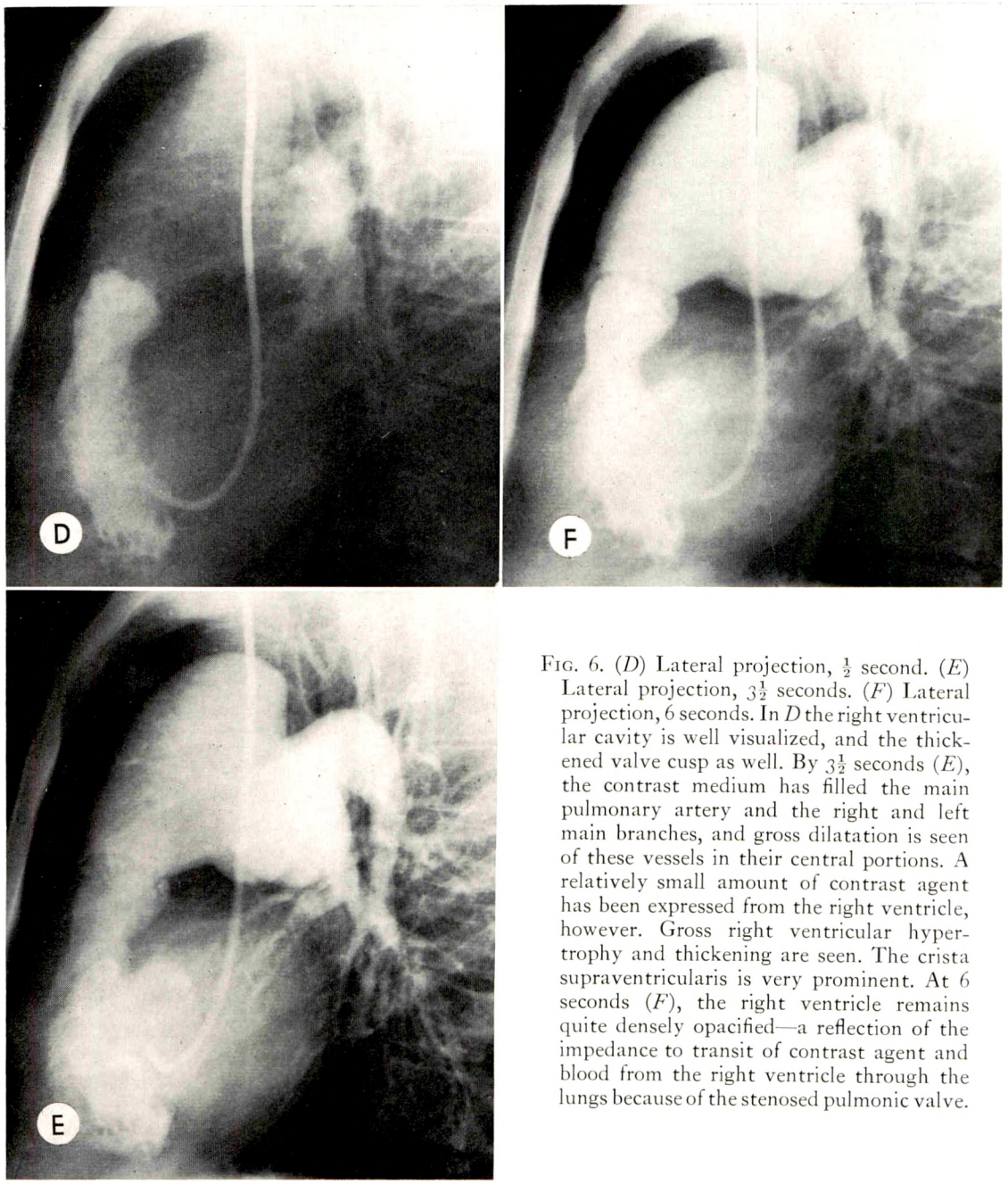


Fig. 6. (*D*) Lateral projection, $\frac{1}{2}$ second. (*E*) Lateral projection, $3\frac{1}{2}$ seconds. (*F*) Lateral projection, 6 seconds. In *D* the right ventricular cavity is well visualized, and the thickened valve cusp as well. By $3\frac{1}{2}$ seconds (*E*), the contrast medium has filled the main pulmonary artery and the right and left main branches, and gross dilatation is seen of these vessels in their central portions. A relatively small amount of contrast agent has been expressed from the right ventricle, however. Gross right ventricular hypertrophy and thickening are seen. The crista supraventricularis is very prominent. At 6 seconds (*F*), the right ventricle remains quite densely opacified—a reflection of the impedance to transit of contrast agent and blood from the right ventricle through the lungs because of the stenosed pulmonic valve.

ably due to hypertrophy of the crista supraventricularis, was evident. The cardiac output had risen as compared with preoperative figures.

DISCUSSION

In his classic paper on localization of cardiac calcifications, Sosman[15] noted a case of pulmonary valve calcification recognized at autopsy. Bouvrain and Bescol-Liversac[2] referred to a case, but without amplification. Brock,[3] in a discussion of congenital pulmonic stenosis with intact ventricular septum, stated that "in late cases the small orifice may carry warty vegetations or even be calcified; exceptionally the valve may be calcified." McGinnis *et al.*[12] have re-

ported a case of calcific pulmonic stenosis in a 49 year old man, in whom laminagraphy demonstrated the calcification. There was no allusion to surgical or pathologic verification in this case. Textbooks on cardiac pathology and diagnosis emphasize the rarity of pulmonic valve calcification. Calcific deposits gross enough to be detected on roentgenologic study are almost unique, only one prior case having been illustrated in the literature.[12]

Because there is relatively little familiarity with this lesion, the points of differentiation from certain other intracardiac calcifications deserve emphasis. Aortic valve calcification may represent the greatest source of confusion, particularly since both lesions produce a systolic murmur at the base of the heart and frequently a cardiac silhouette that is not significantly outside the normal range. Figures 1–4, inclusive, illustrate the differences both in the cardiac silhouette and in the location and appearance of the valve calcification. Poststenotic dilatation of the pulmonary artery is visible in the frontal and right anterior oblique projection (Fig. 1, *A* and *B*); in contrast, poststenotic dilatation of the aorta is best seen in the left anterior oblique projection (Fig. 2*C*). The over-all heart size is slightly increased in the case of pulmonic stenosis, with some prominence of the right atrial border and posterior displacement of the left ventricle in the left anterior oblique projection (Fig. 1*C*); in contrast, the heart is normal in size with slight rounding of the left ventricular contour in the left anterior oblique projection (Fig. 2*C*) as an indication of concentric hypertrophy. The pulmonary valve calcification is visible in a position which is anterior and relatively superior (Fig. 1, *B* and *D*; and 3, *A* and *B*); in the lateral projection the valve plane is more or less horizontal. Aortic valve calcification is clearly more posterior in position (Fig. 2*D*; and 4*B*), and somewhat more caudally placed; in the lateral projection the valve plane is oblique rather than horizontal. At fluoroscopy the aortic valve calcifications have greater excursions with ventricular systole and diastole than do those of the pulmonic valve.

Although the lateral is the single best position for localization of pulmonic valve calcification, the right anterior oblique view is also helpful. In the frontal projection the calcification may be superimposed on the vertebral column and the costal cartilages,[13,14] and in the left anterior oblique projection it is difficult to separate from the aortic valve. Cinefluorography is the best method in our judgment of studying intracardiac calcifications,[9] and using this technique, a few short strips in different projections are adequate.

In evaluating valve calcification, it should be kept in mind that the position of the valves in order from front to back is as follows: pulmonic valve, tricuspid valve, aortic valve, and, most deeply placed within the heart, the mitral valve.[11] The tricuspid valve, however, is only slightly anterior to the aortic valve. The tricuspid valve is more caudally placed, and the mitral valve both posterior and caudal in relationship to the pulmonic valve.

In addition to the valves, other types of calcification such as that in the left atrial wall or thrombus, the left ventricular myocardium or endocardium, the pericardium, the coronary arteries, and the mitral annulus all require differentiation. The distinguishing characteristics have been described by others.[1,2,5,8,9,12,14]

The factors responsible for calcium deposition in soft tissues remain unclear. That injury is one requisite is apparent. Associated with injury, a change in the pH of the soft tissues may suffice to precipitate calcium out of the plasma locally and to cause accumulation of calcium salts. The kind of injury required varies from trauma to atheromatous change. But it is a matter of some interest that atheromatous change and calcification occur most frequently at sites of branching of the great vessels, where

some turbulence in flow and perhaps wall injury may be expected.

In pulmonic stenosis, the marked degree of poststenotic dilatation of the pulmonary artery is surely a reflection of gross turbulence beyond the valve as the result of the force of ejection through a narrow orifice. The infrequency of calcification of this valve indicates that turbulence must be a minor factor and focuses our attention on inflammation.

Mitral and aortic valve calcifications are frequently on the basis of rheumatic valvulitis. The pulmonic valve is generally considered an unusual site of rheumatic disease. Yet, in one series of cases of active rheumatic disease of the heart studied at autopsy, over 50 per cent of the cases demonstrated an interstitial valvulitis of the pulmonic valve.[10] If these figures are correct, then the obvious inference is that acute valvulitis is uncommonly followed by permanent scarring and deformity of the pulmonic valve, in contrast to the aortic and mitral valve. This implies that a combination of inflammation *and* subsequent deformity are requisites for calcification.

Clearly, however, inflammation is by no means the sole factor involved in valve calcification, as is apparent from the data on congenital aortic stenosis. In Campbell and Kauntze's[4] series of patients, calcification developed in increasing numbers in the third to fourth decades. Why should calcification occur in congenital stenosis of the aortic valve but not in the pulmonic valve?

The point has been emphasized that patients with pulmonic stenosis die early in life, and that therefore sufficient time has not elapsed between birth and death for calcium deposits to appear. But more and more patients with pulmonic stenosis are living into the third, fourth and fifth decades with no evidence of valve calcification, while patients with aortic stenosis may develop calcification precisely during this period.

Another factor which requires consideration is the contrast between the relatively high pressure systemic circulation and the low pressure pulmonary circulation. The possibility must be entertained that the high systolic pressure under which blood is expelled from the left ventricle through the aortic valve, and the greater stress to which this valve is consequently exposed, may predispose a congenitally deformed aortic valve to calcification. That this need not be a significant factor is indicated by the absence of calcification in the stenosed pulmonic valve in spite of right ventricular pressures which equal or surpass the systemic in many cases.

A final factor relates to the lower oxygen saturation of the blood in which the pulmonary valve is bathed. But the tricuspid valve, exposed to a similar oxygen concentration, certainly becomes involved by the rheumatic process more frequently than the pulmonic valve and calcifies more frequently. Furthermore, there is no evidence of increased rheumatic pulmonary valvulitis or calcification in the presence of atrial or ventricular septal defects with elevated right ventricular and pulmonary artery oxygen saturation.

In the present case, there seems little doubt that at least two factors were involved. In all probability this patient had congenital pulmonic stenosis with gross deformity and thickening of a bicuspid pulmonic valve. Superimposed upon this was a bout of pulmonic endocarditis from which the patient recovered spontaneously. He handled his disease very well until the age of 39 at which time the first signs of right heart failure became manifest. One year later the right ventricular pressure was 193/20 mm. Hg, the systolic pressure being almost double that of the systemic level. Meanwhile, the deformed, fibrotic valve became the seat of extensive calcific deposits.

Thus, in the pulmonic valve, it seems likely that gross calcification will occur only with inflammation superimposed on stenosis and deformity. Since pulmonic

endocarditis is relatively unusual, calcific pulmonic stenosis is, correspondingly, a rare lesion.

SUMMARY

Calcific pulmonic stenosis is a rare entity. The case of a 40 year old man with extensive calcification of the pulmonic valve is recorded, together with the clinical, roentgenologic, angiocardiographic, cardiac catheterization, surgical and pathologic data. Pulmonic valve calcification is more anterior in location and somewhat more cephalad than aortic valve calcification. It is best demonstrated in the lateral and in the right anterior oblique projections. Localization and possible etiologic factors are discussed.

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VOL. 89, NO. 2

PULMONARY EMBOLISM*

ROENTGENOGRAPHIC AND ANGIOGRAPHIC CONSIDERATIONS

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IN RECENT reports pulmonary embolism is stated to be the most common acute pulmonary disease encountered in hospital practice.[33] With the advent of a practical thoracic surgical approach for direct treatment of pulmonary embolism,[6,7,32] the added importance of an accurate diagnosis of this entity is obvious. The usual clinical methods of diagnosis of pulmonary embolism may be inconclusive. Routine roentgenographic studies show wide variation, and in a large number of patients abnormal findings may be nonexistent. The radiologist suggested the diagnosis of pulmonary embolism, as reported by Stein *et al.*,[33] in only 54 per cent of a series of 72 cases.

ROUTINE ROENTGENOGRAPHIC FINDINGS

In order to appreciate fully the reliability of the routine roentgenogram in pulmonary embolism, the abnormal findings should be divided into those resulting from pulmonary infarction and those in which an infarction has not occurred from the embolic episode. It is well known that pulmonary infarctions are common in the presence of pulmonary congestion as seen in left ventricular heart failure and lesions of the mitral valve. However, Arendt and Rosenberg[1] state that only about 50 per cent of all patients clinically suspected of pulmonary emboli have infarction. In a review of 3,000 autopsies, Schinz *et al.*[27] found 200 hemorrhagic pulmonary infarcts and 209 pulmonary emboli without infarction. This is further substantiated by correlating the findings on routine roentgenograms with those on pulmonary angiograms (Table 1). The roentgenograms of the patients suspected of having an acute embolism showed compatible findings in only 47 per cent of cases. It readily becomes apparent that a considerable portion, approximately 50 per cent, of the patients with pulmonary emboli will not show the typical roentgenographic findings of infarction.

The routine roentgenographic changes indicative of pulmonary infarction, however, should not be minimized and a review of the abnormalities encountered is in order. Stein *et al.*,[33] in a review of 72 postmortem studies of pulmonary infarction, found pleural effusion to be the most common finding, occurring in 46 per cent of cases. Less frequent abnormalities were parenchymal opacifications, which were described as homogeneous, linear, and patchy densities, diaphragmatic elevation, and cavitation. Another observation on the roentgenogram may be a fusiform dilatation of an obstructed pulmonary arterial branch. This may or may not be associated with infarction.

Stein *et al.*[33] also observed that the infarction was manifested on roentgenograms in 22 of 27 patients studied within the first 24 hours following onset of symptomatology.

TABLE I

PULMONARY EMBOLISM

	No. of Cases	Positive Angiograms (per cent)	Positive Angiograms with Negative Roentgenograms (per cent)
Acute*	26	73	47
Recurrent	22	41	22

* Two incomplete studies are not included (see text).

* From the Departments of Radiology and Medicine, Cardiopulmonary Division, The University of Texas Southwestern Medical School and Parkland Memorial Hospital, Dallas, Texas.

Pulmonary infarctions are consistently observed to be most common within the lower lobes.

The homogeneous parenchymal opacifications resulting from pulmonary infarction may vary considerably in size and shape. Initially, as noted by Hampton and Castleman,[10] the parenchymal infarction may be ill defined and indistinguishable from bronchopneumonia. Subsequently, the area of infarction becomes more discrete as contraction occurs. The shape of the involved

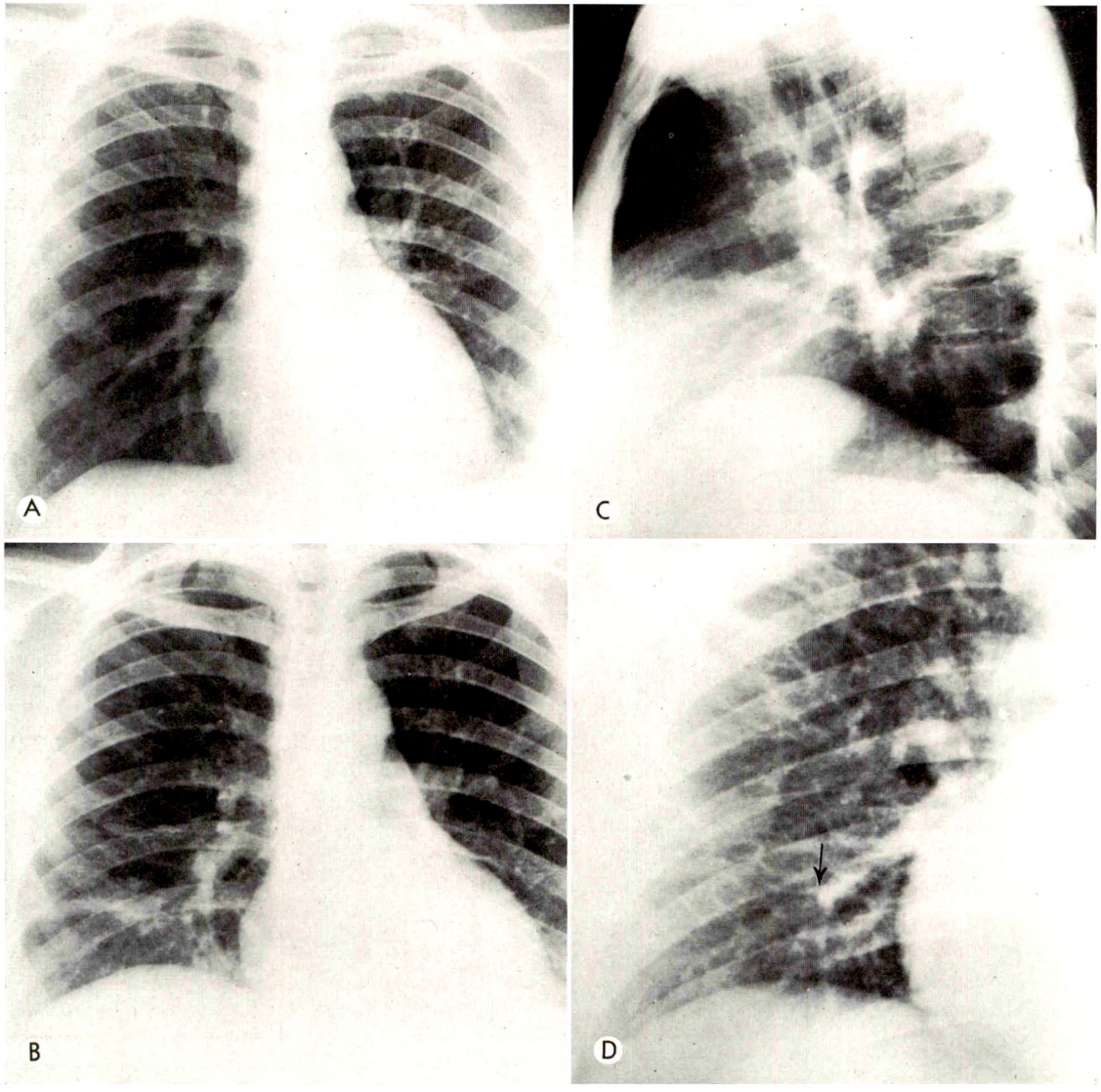


FIG. 1. (*A*) Routine chest roentgenogram during gestation showing a normal lung vasculature. An artifactual highlight is noted within the left base. (*B* and *C*) Frontal and lateral roentgenograms following an episode of chest pain reveal two areas of linear opacification, one in the lateral segment of the right middle lobe and the other in the areas of anterior and lateral segments of the right lower lobe. The frontal study shows fusiform dilatation of the descending branch of the right pulmonary artery. (*D*) Close-up of the pulmonary angiogram, 3 weeks later, shows an obstruction (indicated by arrow) of the descending branch of the right main pulmonary artery at the origin of the branches supplying the lateral segment of the right middle lobe and anterior and lateral segments of the right lower lobe. The fusiform dilatation of the opacified artery as well as the parenchymal opacification noted in *B* has disappeared.

area may be the typical triangular opacification; however, an elongated linear density is present at times. Arendt and Rosenberg[1] described a rounded opacified infarction having a "parachute" shape, with indented edges and the base resting on a pleural surface. As the opacifying infarction contracts, it becomes roentgenographically more dense and shows better demarcation. Resolution as followed on the serial roentgenograms varies from days to many weeks.

Several of the findings on the chest roentgenogram resulting from infarction are seen in Figure 1, *A–D*, the case of a 23 year old pregnant Negro woman. The chest roentgenogram (Fig. 1*A*) at the time of gestation showed the lung fields to be clear. Note the normal size and shape of the descending branch of the right main pulmonary artery. The frontal and lateral projections of this patient (Fig. 1, *B* and *C*) following an episode of chest pain after delivery demonstrated two areas of linear opacification, one in the lateral segment of the right middle lobe and the other in the areas of the anterior and lateral segments of the right lower lobe. Note on the frontal study that the descending branch of the right main pulmonary artery shows fusiform dilatation. The right diaphragm is slightly elevated. Three weeks after Figure 1, *B* and *C*, a pulmonary angiogram (Fig. 1 *D*) showed a blunt obstruction (arrow) of the descending branch of the right main pulmonary artery at the origin of the arteries supplying the lateral segment of the right middle lobe and the anterior and lateral segments of the right lower lobe. The fusiform dilatation of this artery has subsequently resolved as has most of the parenchymal opacification.

Other findings of infarction on the routine roentgenogram are exemplified in the following cases. The routine roentgenogram (Fig. 2*A*) of a 34 year old Negro female during gestation showed normal vasculature within the right lung field. Three months later, following symptoms of a pulmonary embolus, a relative radiolucency of the right lung with diminution in visible

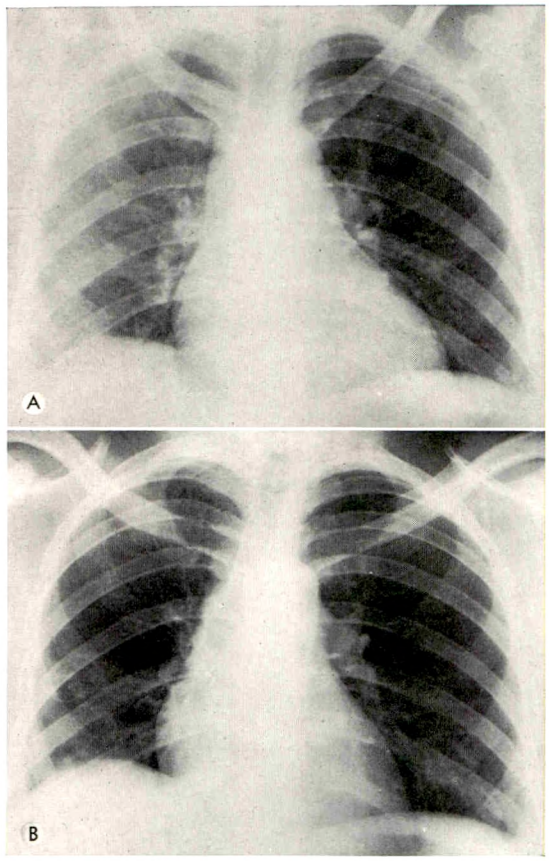


Fig. 2. (*A*) Routine roentgenogram of a 34 year old Negro female during gestation showing normal hilar vascular markings. (*B*) Chest roentgenogram 3 months following *A* shows a relative radiolucency within the right lung and absence of hilar vascular markings. The right diaphragm is elevated. Within the lateral segment of the right middle lobe, an excavatory process measuring 3 × 2.5 cm. is present.

hilar and peripheral pulmonary vasculature was visualized (Fig. 2*B*). The right diaphragm was elevated, indicative of volume loss of the right lung. There was an excavatory process measuring 3.0 by 2.5 cm. in the region of the lateral segment of the right middle lobe, a significantly small infarction as compared to the magnitude of the vascular obstruction. The pulmonary angiogram (Fig. 2*C*) at this time revealed a complete obstruction of the right main pulmonary artery. A significant angiographic finding was the tapering of the right main pulmonary artery indicative of organization of the embolus within the artery. A retro-

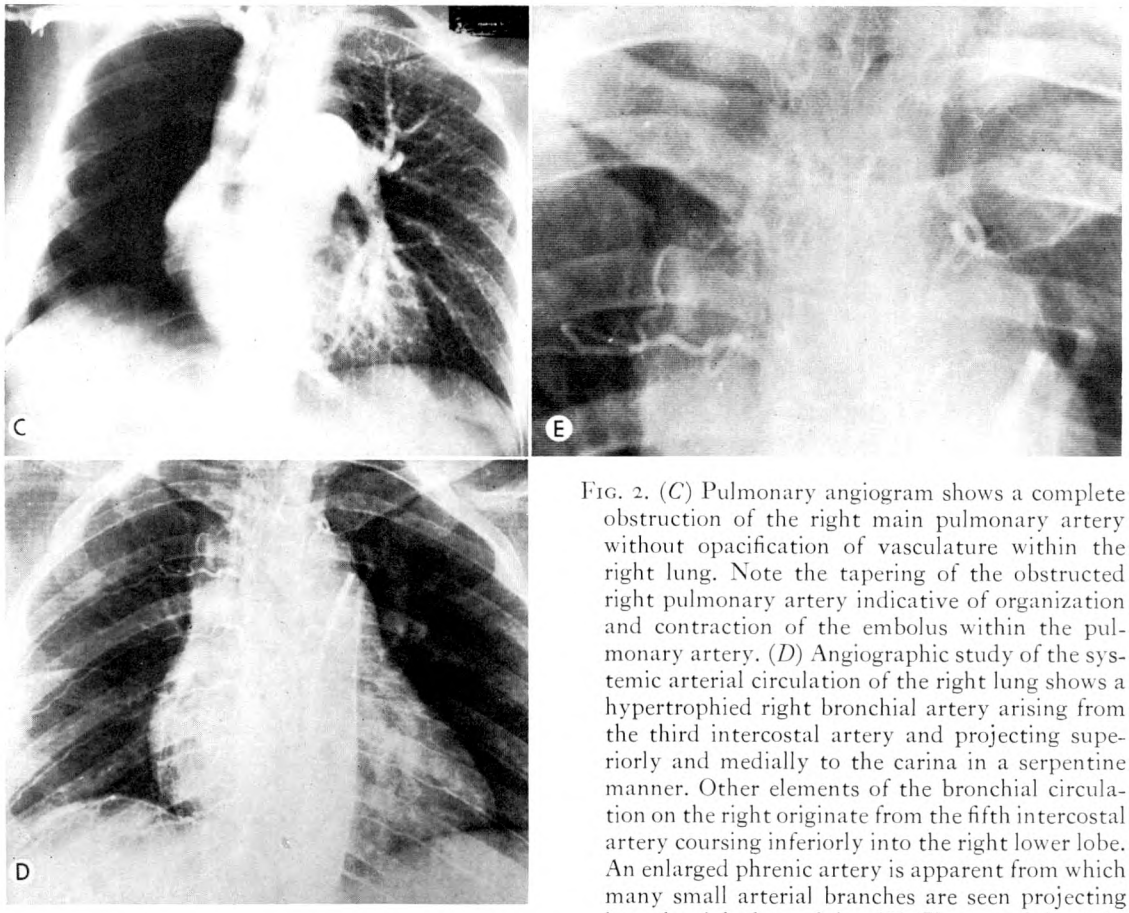


FIG. 2. (*C*) Pulmonary angiogram shows a complete obstruction of the right main pulmonary artery without opacification of vasculature within the right lung. Note the tapering of the obstructed right pulmonary artery indicative of organization and contraction of the embolus within the pulmonary artery. (*D*) Angiographic study of the systemic arterial circulation of the right lung shows a hypertrophied right bronchial artery arising from the third intercostal artery and projecting superiorly and medially to the carina in a serpentine manner. Other elements of the bronchial circulation on the right originate from the fifth intercostal artery coursing inferiorly into the right lower lobe. An enlarged phrenic artery is apparent from which many small arterial branches are seen projecting into the right lower lobe. (*E*) Closeup of the right bronchial artery arising from the third intercostal artery. (*C*, *D* and *E* reproduced by courtesy of *Radiology*.[41])

grade aortogram (Fig. 2*D*) showed the significance of the systemic arterial circulation in prevention of diffuse infarction of this right lung. The hypertrophied right bronchial artery arises from the third intercostal artery and courses superiorly and medially to the carina, showing many tortuous opacified branches. Other elements of the bronchial circulation on the right originate from the fifth intercostal artery and extend into the right lower lobe. Numerous branches from an enlarged right phrenic artery project into the right lower lobe. The significance of the intercostals in such a case is evident by their marked tortuosity on the right as compared to the normal linear left intercostal arterial system. Figure 2*E* shows a close-up of the hypertrophied right bronchial artery derived from the third intercostal, and the serpiginous appearance as it approaches the hilus.

Another case of apparent massive pulmonary artery obstruction is shown in Figure 3, *A* and *B*, the roentgenograms of a 61 year old female. The initial routine roentgenographic study (Fig. 3*A*) following clinical symptoms compatible with pulmonary embolism revealed a homogeneous right hilar density with a pleural effusion. Serial roentgenograms disclosed progressive opacification of the right lung, and, at 21 months following the initial study, the chest roentgenogram (Fig. 3*B*) showed considerable diminution in the right hemithorax and irregularly opacified areas representing infarction within the right lung. Comparing this case with that of Figure 2,

the patient's age probably prevented significant compensatory hypertrophy of the bronchial arterial system, and thus progressive infarction of the right lung occurred.

For patients who have pulmonary emboli without infarction other roentgenographic manifestations must be considered. Westermark[38] has emphasized the findings of an ischemic lung. Accordingly, the involved lung shows a paucity of vasculature with a relative radiolucency. This sign of embolism has been observed to be quite subtle and extremely difficult to interpret with technical factors affecting variations. If previous roentgenograms of the patient are available, this observation may become less tenuous (Fig. 2, *A–E*).

Three cases of pulmonary embolism without infarction have been observed by Shapiro and Rigler[30] to show ipsilateral increased radiolucency, abrupt termination of the vascular pattern, and diaphragmatic elevation. The presence of emboli was confirmed on postmortem study.

Felson[8] presented a case of embolism in which the prominent finding was a small hilus. No infarction resulted and apparently recanalization occurred as the roentgenogram showed normal hilar vascular markings 17 days later.

As described by Schulze,[28] vascular obstruction may cause secondary changes of diminished volume of the involved lung with resultant relative diaphragmatic elevation (see Fig. 2, *A–E*). Contrasted to primary ventilatory disease, the mediastinum may move to the homolateral side.

It is well known that acute or recurrent massive pulmonary embolism may lead to cor pulmonale. Rapid enlargement of the main pulmonary artery which may precede cor pulmonale is a most important roentgenographic finding indicating massive or recurring pulmonary emboli.

The initial roentgenogram (Fig. 4*A*) of a 21 year old female showed a parenchymal opacification within the right lower lobe. This finding was roentgenographically compatible with either a pneumonia or pulmonary infarction. Subsequent study 9 days later (Fig. 4*B*) revealed partial clearing of the parenchymal density. However, significant enlargement of the pulmonary artery as compared to the previous study was apparent. This patient succumbed and

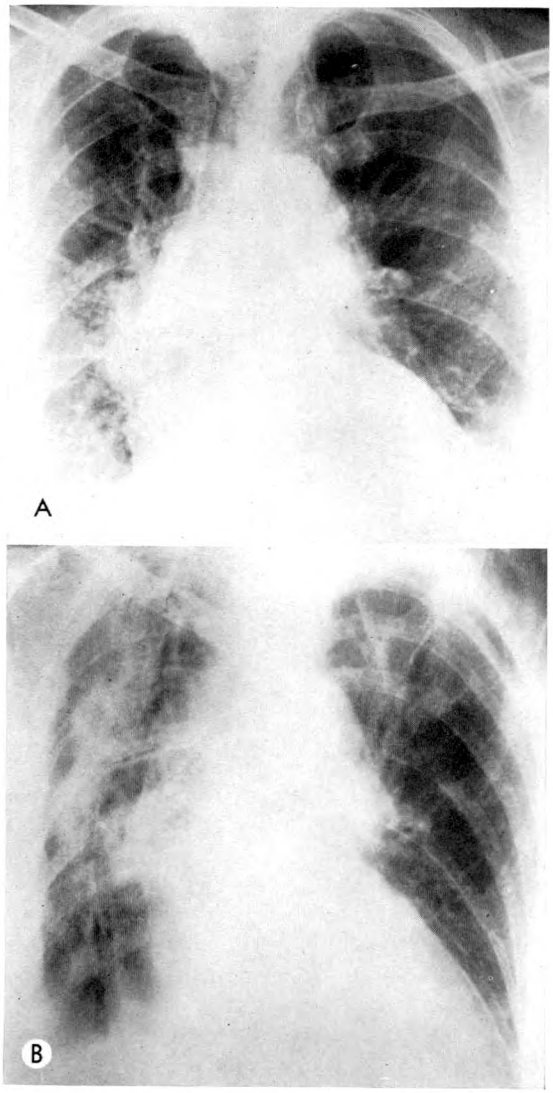


Fig. 3. (*A*) *December 15, 1957:* An initial chest roentgenogram following clinical symptoms compatible with pulmonary embolism showing a large homogeneous right hilar density and pleural effusion. (*B*) *September 28, 1959:* Roentgenographic study 21 months following *A* shows progressive opacification of the right lung with diminution in the right hemithorax. The parenchymal opacification represents infarction. Findings of right main pulmonary artery obstruction with massive infarction were noted at postmortem study.

at postmortem examination a large embolus was noted within the left pulmonary artery. This rapid enlargement of the pulmonary artery has been observed in other cases of pulmonary emboli, either from a large single embolus or, more frequently, from multiple recurrent emboli.

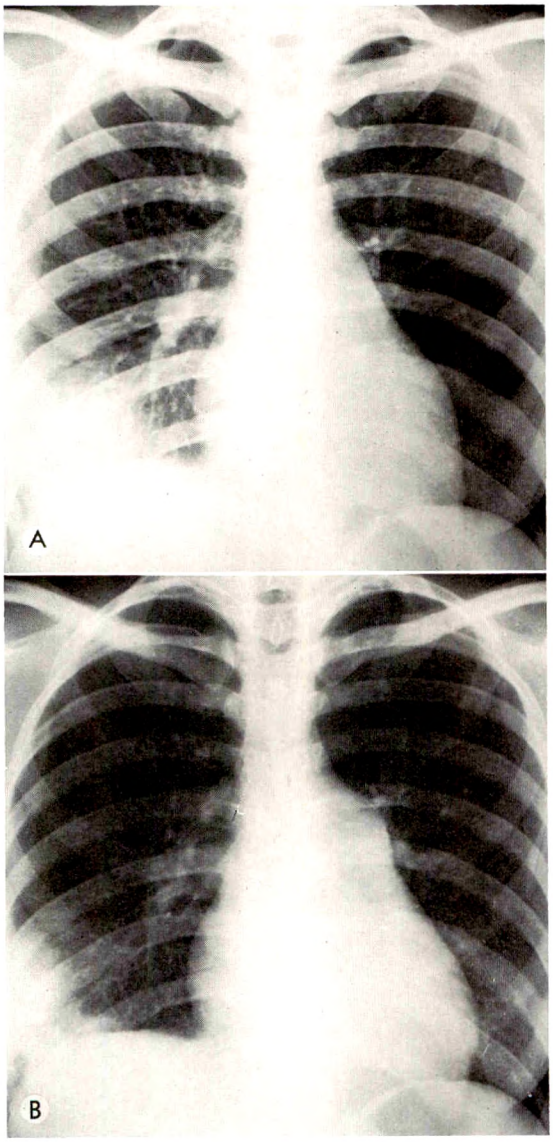


FIG. 4. (*A*) *February 12, 1960:* Chest roentgenogram showing a parenchymal opacification within the right lower lobe. Note the contour of the main pulmonary artery. (*B*) *February 21, 1960:* Chest roentgenogram 9 days following *A* shows marked accentuation of the main pulmonary artery, indicative of an acute pulmonary hypertension. The parenchymal opacification within the right lower lobe shows partial resolution. Postmortem study showed a large embolus within the left main pulmonary artery and the finding within the right base represented pneumonia.

PULMONARY ANGIOGRAPHY

The Robb-Steinberg angiographic technique[25,26] was chosen primarily for the rapidity with which it can be accomplished. The patient with acute pulmonary embolism is often seriously ill or even moribund, and this technique can be done expeditiously with minimal preparation and manipulation of the patient. There is no time required for fluoroscopy and placement of catheters. Manipulation of possible thrombi within the upper extremity or superior vena cava or other areas traversed by the catheter is eliminated although, as is well known, most emboli originate in the lower extremities. In a series of 50 cases (Table 1), all patients have tolerated the procedure well. Two studies were inconclusive due to lack of patient cooperation or to dilution of the medium, the result of cardiomegaly with arrythmia.

Interpretation of the pulmonary angiogram is done by detailed viewing of the pulmonary vessels. The interpreter must be familiar with the "end on" appearance of the branching pulmonary arteries which may simulate a blunt obstruction. Most angiograms are made with the patient supine in an anteroposterior projection; however, varied oblique roentgenograms on subsequent injections may be necessary to delineate a questionable area.

Pulmonary emboli are manifested on the angiogram in many ways. For purposes of discussion, these will be divided into the emboli within the two main branches of the pulmonary artery and the remainder of the pulmonary arterial branches.

Within either the right or left main pulmonary artery, the angiographic appearance is determined by the longevity of the obstructing embolus. As seen in Figure 2*C*, the angiographic study demonstrates complete obstruction of the right main pulmonary artery with the area of obstruction

showing a tapering—indication of circumferential organization of the embolus and contraction. No opacification distal to this point is seen within the right pulmonary arterial tree, indicative of a complete obstruction. On the contrary, an acute case of major pulmonary arterial block is seen in Figure 5, *A* and *B* in which the history revealed the embolic episode to have occurred some 8 days prior to angiography. The routine roentgenogram (Fig. 5*A*) shows a small parenchymal density, compatible with infarction in the left base. The left pulmonary artery on the angiographic study (Fig. 5*B*) is noted to be of normal diameter, but there is a filling defect within the opacifying medium. The inferior portion of this main pulmonary artery shows faint opacification; this is indicative of incomplete adherence of the embolus to the pulmonary artery. Distal to this obstruction, there is opacification of the pulmonary arterial tree in the left upper lung field even though the vessel caliber is decreased, indicative of diminution in flow to this area. Complete peripheral vascular obstructions are noted in the left lower lobe and within a portion of the right lower lobe as evidenced by diminished opacified vasculature. Emphasis must be placed on interpretation of the opacified vessel in order to determine the degree of organization of the embolus when direct thoracic surgical approach is contemplated.

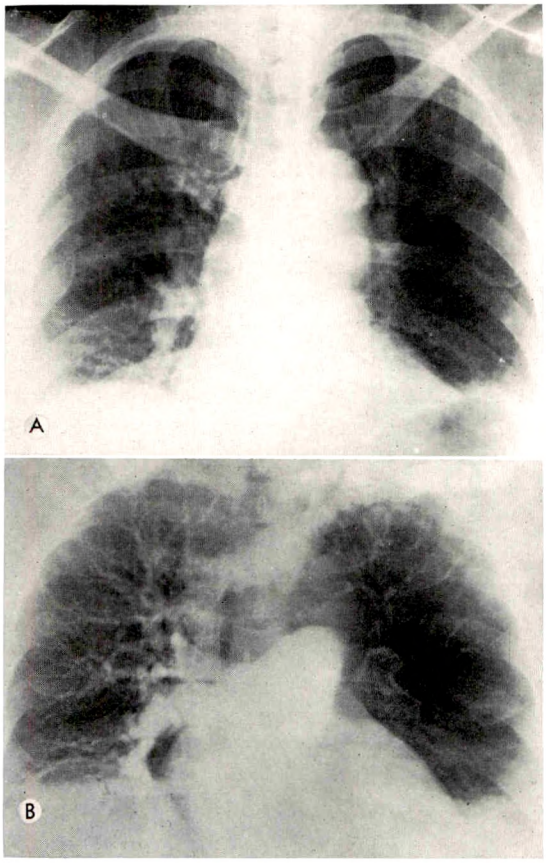


Fig. 5. (*A*) Chest roentgenogram shows a small parenchymal opacification adjacent to the diaphragm within the left base. (*B*) Pulmonary angiogram reveals a large defect within the left main pulmonary artery representing embolus. There is incomplete obstruction, as peripheral vasculature within the left upper lobe and lingula is faintly opacified. The left main pulmonary artery is of normal diameter. An area of diminished opacified vasculature is seen within the right lower lobe secondary to a smaller obstructing embolus.

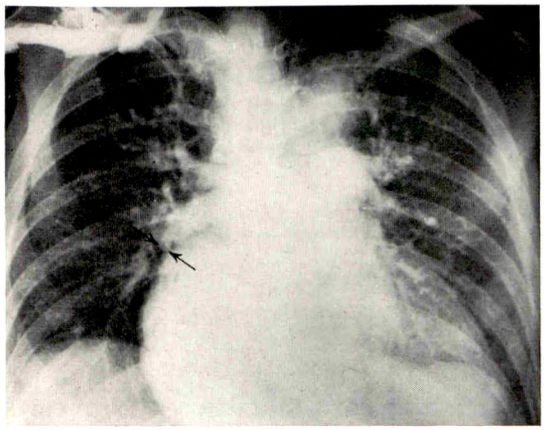


Fig. 6. Pulmonary angiogram showing blunt obstruction (indicated by arrows) of the arterial branch supplying the medial segment of the right middle lobe.

Smaller peripheral emboli are obviously more difficult to detect on the angiogram. They may exhibit varied changes on the contrast study. A blunt obstruction of the peripheral vessel is shown in Figure 6.

Other findings may be irregularly diminished arterial caliber and a paucity of opacified small vessels. This latter manifestation is best appreciated in the late pulmonary arterial and early venous phase of

the angiogram, thus enabling the interpreter to better compare the questionable area. Figure 7, an oblique pulmonary angiogram, shows such a change in the late pulmonary arterial phase. Within the superior segment of the right lower lobe and left base no opacified vessels are seen, indicating vascular obstruction. These areas of relative radiolucency on the angiogram must be differentiated from pulmonary emphysema. In the emphysematous cases the adjacent vasculature will frequently show either displacement, elongation or the typical "wintery tree" appearance.

DISCUSSION

The roentgenographic approach to diagnosis of pulmonary embolism is obviously an important one. Following the above review, however, it becomes apparent that approximately 50 per cent of the patients fail to show embolic changes on the routine roentgenogram and therefore it behooves one to resort to the angiographic approach for complete evaluation of the patient suspected of pulmonary embolism.

Evaluation of the contribution of the pulmonary angiogram in patients in whom routine roentgenographic studies show findings compatible with infarction must be considered. As previously stated, routine findings may not indicate location or the extent of embolism. As shown in Figure 5, *A* and *B* a very small area of infarction is seen on the routine roentgenogram while the angiogram shows massive embolism.

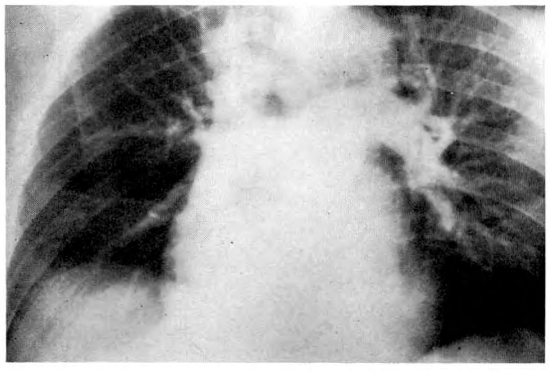


FIG. 7. An oblique pulmonary angiogram showing absence of opacified vessels within the superior segment of the right lower lobe and the left base; both areas are indicative of vascular obstruction.

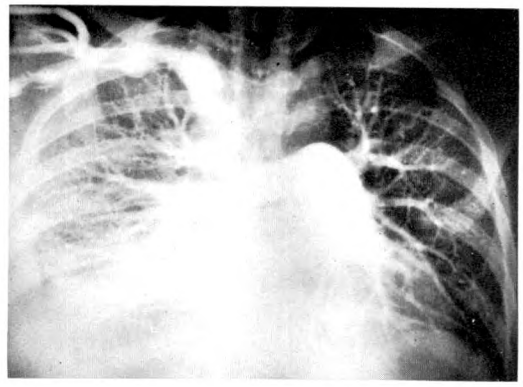


FIG. 8. Pulmonary angiogram in the presence of a right pleural effusion shows good opacification of the pulmonary vascular tree on the right indicating patency. The vasculature appears crowded due to volume loss of this right lung. The effusion was found to be due to tuberculosis.

The angiogram may further support or disprove the impression of pulmonary embolic phenomenon. Figure 8 is the case of a young Negro female who 10 days post partum presented with right chest pain. The routine roentgenogram revealed a right pleural effusion. The angiogram shows good vascularization of a right lung which was compressed by the effusion. This angiographic study failed to reveal findings of embolism and clinical work-up subsequently showed the etiology of the effusion to be tuberculosis.

Pulmonary angiography has also been done for evaluation of those patients with idiopathic pulmonary hypertension or with roentgenographic findings compatible with chronic recurrent embolism. The anticipated positive results in these patients as seen in Table 1 would obviously be less than those seen acutely. The angiogram is still important in treatment planning of these patients.

SUMMARY

The contributions and limitations of the routine chest roentgenogram in pulmonary embolism both with and without infarction

have been discussed in detail. The importance of the use of pulmonary angiography for more accurate roentgenographic analysis of these cases is stressed. The angiographic abnormalities resulting from pulmonary embolism in a series of 50 clinically suspected cases are enumerated.

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ROENTGENOGRAPHY OF SYSTEMIC (CONGENITAL AND TRAUMATIC) ARTERIOVENOUS FISTULAS*

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ARTERIOVENOUS fistulas apparently occur wherever there are arteries and concomitant veins. Indeed, congenital arteriovenous fistulas have been described in practically every tissue, organ and limb.[9,10] Trauma, either direct or indirect, is another cause of arteriovenous fistulas. Many cases have followed gunshot and stab wounds, especially after surgical procedures.[7,8] Contrast roentgenography by which arteriovenous fistulas can be visualized significantly contributes to the diagnosis and surgical treatment of such lesions. This is illustrated by the 14 selected patients herein reported who were recently studied at The New York Hospital—Cornell Medical Center.

MATERIAL AND METHODS

Table 1 lists the clinical, roentgenographic, and follow-up data of a selected group of 14 patients with systemic arteriovenous fistulas encountered at this center during a 12 year period. Central nervous system arteriovenous fistulas were not included because they are chiefly the concern of neurosurgeons. Nineteen patients with pulmonary arteriovenous fistulas were also not included because they presented different problems. Their angiocardiographic diagnosis and surgical treatment have recently been reviewed.[13] Although many patients with multiple arteriovenous fistulas of a limb have been studied at this center, only a single patient (Case IV) is presented in this report. This is because treatment for this type of arteriovenous fistula is often futile and, as in our case, frequently requires amputation of the involved limb.[3]

Nine of the 14 patients had selective visualization of an arteriovenous fistula by the use of a catheter or needle inserted into an artery. When a catheter was employed, it was advanced to the site of the arteriovenous fistula. Dilute contrast material was then injected, usually by hand, and serial roentgenography was performed.[2] In only 3 instances (Case VIII, XI and XII) was a pressure injector (Gidlund) used. Intravenous angiocardiography was the sole method by which visualization of the arteriovenous fistula was obtained in 5 instances (Cases II, V, IX, X and XIII). In 4 patients both intravenous angiocardiography and selective arteriography were performed (Cases III, IV, VI and XII). In Case III, the intravenous technique of carotid-vertebral arteriography was the method used to visualize the scalp arteriovenous fistula.[12]

In 8 of the 14 patients herein reported, the arteriovenous fistula was congenital. Two patients (Case I and II) had arteriovenous fistulas involving the right shoulder (Fig. 1, *A* and *B*; and Fig. 2, *A* and *B*). One patient had an arteriovenous fistula of the scalp (Case III) (Fig. 3, *A* and *B*); another had multiple fistulas of the entire left leg (Case IV) (Fig. 4, *A* and *B*). Three had coronary arteriovenous fistulas (Case V to VII) (Fig. 5, *B*, *C*, and *D*; and Fig. 6, *B* and *C*). Case VIII is unique in that a congenital lumbar arteriovenous fistula was demonstrated (Fig. 7, *A–D*). Operations, right

(*Text continued on page 349*)

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Case No.	Age (yr.)	Sex	Year	Reference No.	Complaint	Physical Examination	Conventional Roentgenogr of the Chest
I	22	F	1951	1	Enlarging mass of right interscapular area since childhood	Thrill and continuous bruit over right shoulder	Normal
II	19	F	1961	15	Thrill of right side of back	Continuous murmur and thrill of right shoulder; tachycardia	Normal
III	28	M	1959		Mass of right side of head since birth	Pulsatile 5 by 6 cm. mass anterior to right ear with continuous bruit and thrill; blood pressure 170/110 and tachycardia	Normal
IV	19	M	1960		Ulceration of left knee area	Loud bruit of left patella and knee areas with multiple scars over medial thigh, knee, and popliteal area	Normal
V	6	F	1949	10	Asymptomatic	Continuous murmur in 4th and 5th interspaces at mid-clavicular line	Normal
VI	9	F	1961	5	Heart murmur since birth, frequent upper respiratory tract infections	Continuous machinery murmur over precordium, loudest in 4th interspace along right and left sternal borders with faint thrill	Enlargement of the ri atrium and left ventricle w plethoric lung circulat (Fig. 5*A*)
VII	2½	M	1962		Murmur since birth	Continuous murmur over lower sternum, hypochondrium, and xiphoid regions	Enlarged heart with irregu upper superior border of cardiac silhouette and ri atrium (Fig. 6*A*)
VIII	5 mo.	F	1962		Turner's syndrome (gonadal dysgenesis)	Loud continuous murmur to right of second lumbar spine	Normal
IX	48	F	1957	7	Continuous vibration of right anterior chest with buzzing noise along right side of sternum	Well healed scar of right radical mastectomy; continuous murmur in 2nd right anterior interspace near sternum	Normal
X	46	F	1961	14	Dyspnea, abdominal distention and weakness of 9 months' duration following ruptured disk operation	Enlarged heart and liver, right pleural effusion, ascites, and pitting edema of legs and trunk. Harsh continuous bruit all over thorax as far as popliteal spaces, loudest over right groin; increased venous pressure	Enlarged heart; fluid in ri lung base (Fig. 9, *A* and *B*
XI	62	M	1961		Jaundice, constipation, and abdominal swelling. In 1960, had right nephrectomy for renal carcinoma	Continuous murmur over the right side of the abdomen, blood pressure 160/74	Normal
XII	67	F	1962		Abdominal pain persistent 1 year after bowel resection for gangrene	Bruit of lower part of abdomen; ascites	Normal
XIII	28	M	1959		Accidental gunshot wound in 1951 resulted in arteriovenous fistula of left leg; operation failed to correct lesion	Continuous bruit and thrill, best heard in lateral mid-calf area	Normal
XIV	55	M	1962		Injured left arm by flying metal chip from ax	Continuous murmur, thrill, and hematoma of left arm and elbow	Normal; tiny metalic fore body in left arm

Type of Angiographic Procedure	Diagnosis	Interpretation of Angiogram	Surgery and Result
rograde right brachial ar-ography	Congenital arteriovenous fistula of right scapular artery and veins	Huge arteriovenous fistula of right scapular area (Fig. 1, *A* and *B*)	Excision of fistula; curative
ultaneous bilateral intra-ous angiocardiography	Congenital arteriovenous fistula of the right thyrocervical arteries and veins	Jet (filling defect) of right subclavian artery and superior vena cava and right thyrocervical arteriovenous fistula (Fig. 2, *A* and *B*)	Excision of arteriovenous fistula of right shoulder; curative
avenous cerebral angio-hy and right temporal ar-ography	Congenital arteriovenous fistula of right scalp	Arteriovenous fistula between right external carotid and temporal arteries and veins (Fig. 3, *A* and *B*)	Excision of arteriovenous aneurysm between the right external carotid and superficial temporal arteries and veins; curative; blood pressure on discharge normal
avenous aortography and femoral arteriography	Arteriovenous fistula between left superficial femoral artery and vein with giant cirsoid venous channels	Massive arteriovenous fistula of left leg (Fig. 4, *A* and *B*)	Excision of arteriovenous fistula, not curative; amputation of leg; curative
avenous angiocardiography	Congenital coronary arteriovenous fistula	Markedly dilated nest of vessels in anterolateral wall of the heart filling simultaneously with ascending aorta	Observed past 10 years; remains asymptomatic
avenous angiocardiography retrograde aortography	Congenital coronary arteriovenous fistula	In frontal view showed filling defect due to a jet of unopacified blood at junction of superior vena cava and right atrium. Larger defect in lower lateral aspect of the right atrium. At time of aortic opacification, an enlarged cluster of vessels opacifying right atrium was seen (Fig. 5, *B* and *C*). Aortography showed tortuous dilated aneurysmal right coronary artery draining into right atrium (Fig. 5*D*)	Temporary occlusion of aneurysmal right coronary artery was well tolerated. Artery, therefore, doubly ligated. Five and 15 months following operation developed postpericardectomy syndrome; complete recovery followed
cutaneous retrograde femo-coronary arteriography	Congenital coronary arteriovenous fistula	Huge left coronary arteriovenous fistula into the right ventricle (Fig. 6, *B* and *C*)	Still under observation, operation planned
rograde femoral aortogra-	Congenital second lumbar arteriovenous fistula	Biplane abdominal aortography revealed lumbar arteriovenous fistula (Fig. 7, *A–D*)	Exploration and excision of arteriovenous fistula; curative
avenous angiocardiography	Postoperative mastectomy arteriovenous fistula of right internal mammary vessels	Arteriovenous fistula of right internal mammary vessels (Fig. 8, *A* and *B*)	Ligation of individual vessels and removal of fistulous vessels and aneurysmal sac; curative
avenous abdominal aortog-hy	Postlaminectomy iliac arterial-inferior vena caval fistula	Right iliac artery-inferior vena caval fistula (Fig. 9, *C* and *D*)	Ligation of right iliac artery, excision of fistula and repair of inferior vena cava; curative (Fig. 9, *E* and *F*)
cutaneous retrograde femo-arteriography	Postnephrectomy right renal artery-inferior vena caval fistula	Right renal arterial-inferior vena caval fistula (Fig. 10)	Excision of fistula and separate ligations of right renal artery and inferior vena cava; curative. Histologically, cancer tissue found in fistula. Alive and well 6/4/62
avenous abdominal aortog-hy and percutaneous femo-retrograde mesenteric ar-ography	Postoperative mesenteric arteriovenous fistula	Mesenteric arteriovenous fistula with portal and coronary venous hypertension (Fig. 11, *A* and *B*)	Excision of fistula, ligation of the mesenteric artery and veins; curative
avenous arteriography	Traumatic arteriovenous fistulas of left lower leg	Arteriovenous fistulas between anterior tibial artery and vein	Quadruple ligation and excision of the fistulas; curative
t brachial arteriography	Traumatic arteriovenous fistula of left arm	Arteriovenous fistula between left brachial artery and vein (Fig. 12, *A* and *B*)	Excision of fistula and repair of vessels; curative

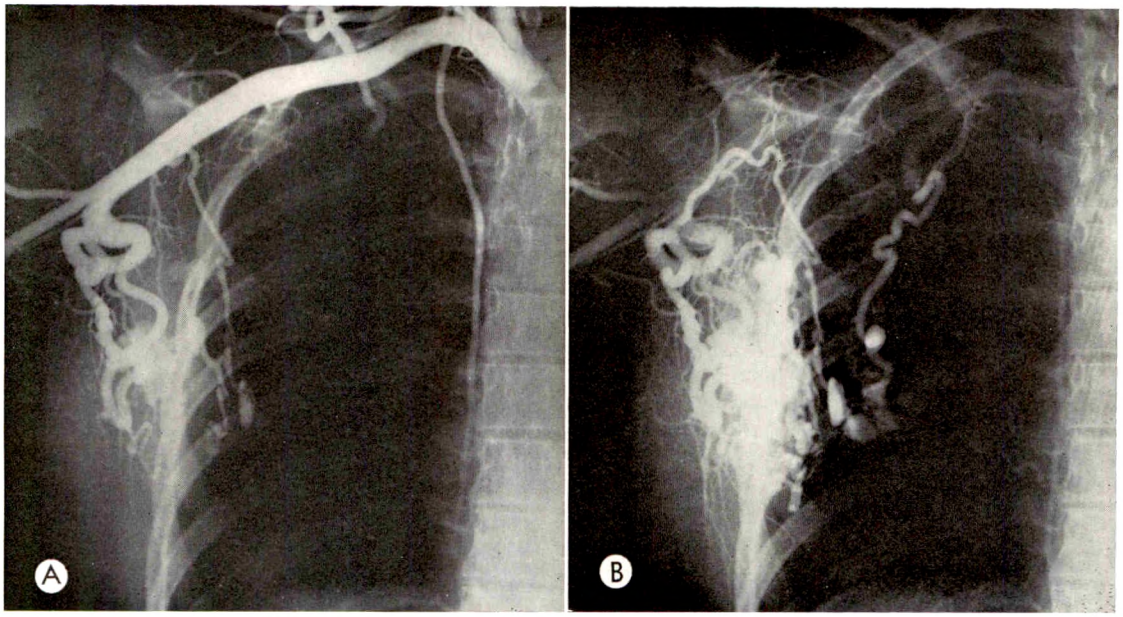


FIG. 1. Case I. Congenital arteriovenous fistula of the right scapula area. (*A*) Retrograde right brachial arteriogram showing the arterial phase of the lesion. (*B*) The arteriovenous component. (Reproduced with permission of the publisher.[1])

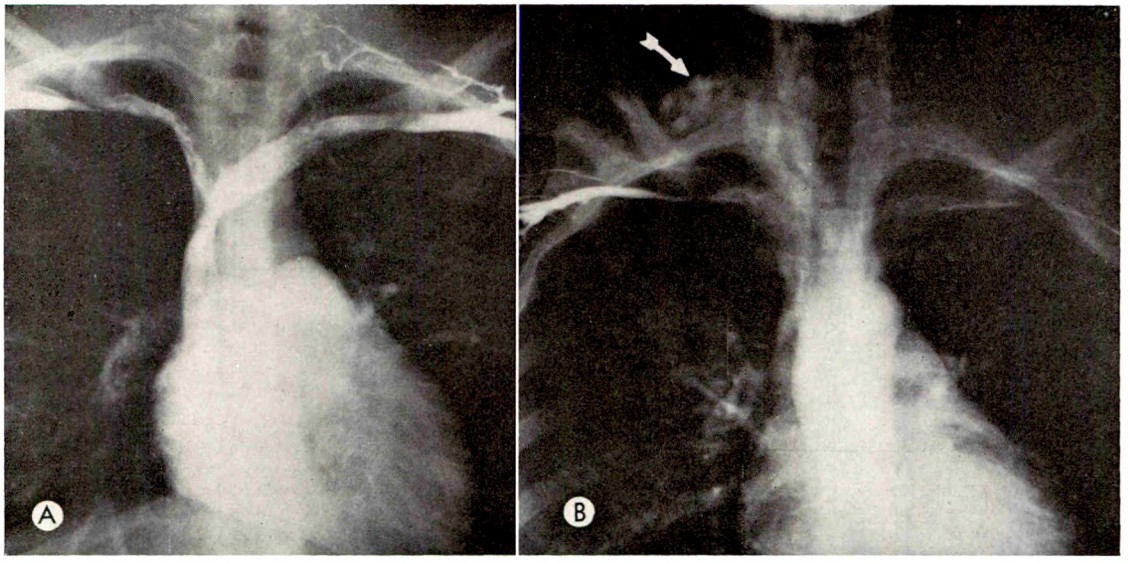


FIG. 2. Case II. Congenital arteriovenous fistula of the right thyrocervical trunk. (*A*) Simultaneous, bilateral angiocardiogram demonstrating filling defect in the right subclavian and innominate veins owing to jets of blood from the right thyrocervical arteries. (*B*) Later stage of *A*, showing the nest of thyrocervical vessels (arrow) and reopacification of the right sublcavian and innominate veins.

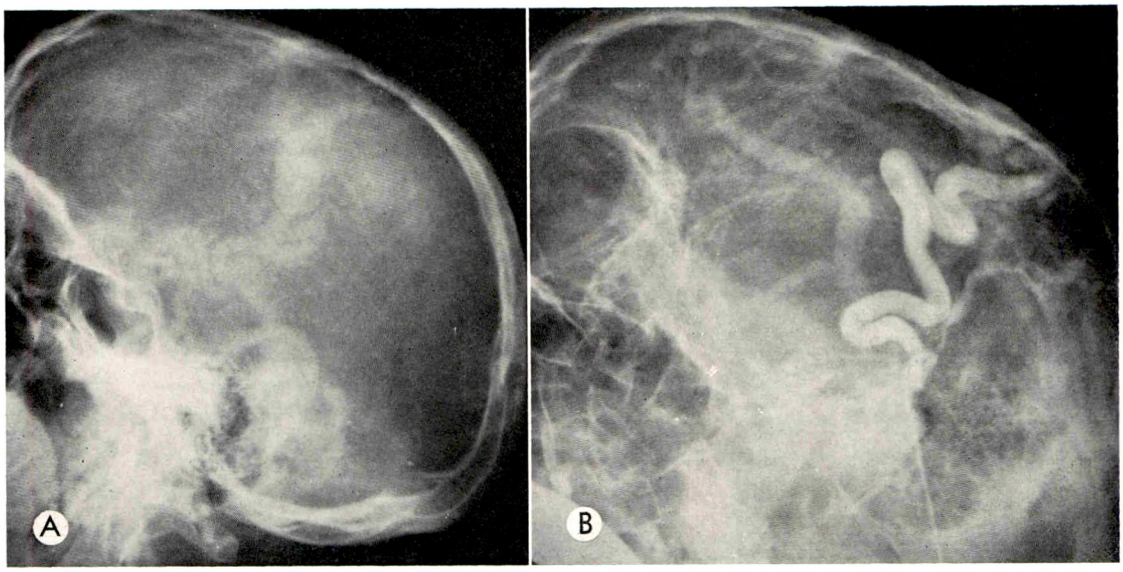


Fig. 3. Case III. Congenital arteriovenous fistula of the right scalp. (*A*) Arteriovenous fistula demonstrated by simultaneous intravenous injection of both arms. (*B*) The lesion demonstrated by direct needle puncture arteriography.

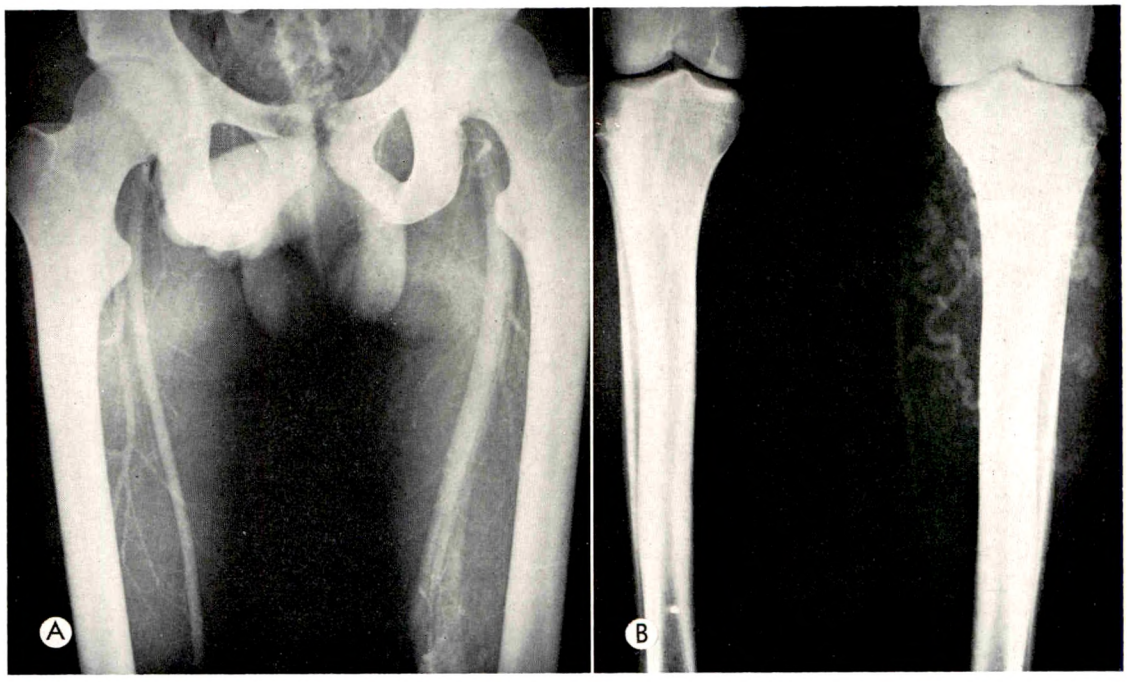


Fig. 4. Case IV. Congenital multiple arteriovenous fistulas of the right leg visualized by the method of intravenous abdominal aortography and peripheral arteriography. (*A*) The pelvis and leg arteriovenous fistulas. (*B*) The knee involvement.

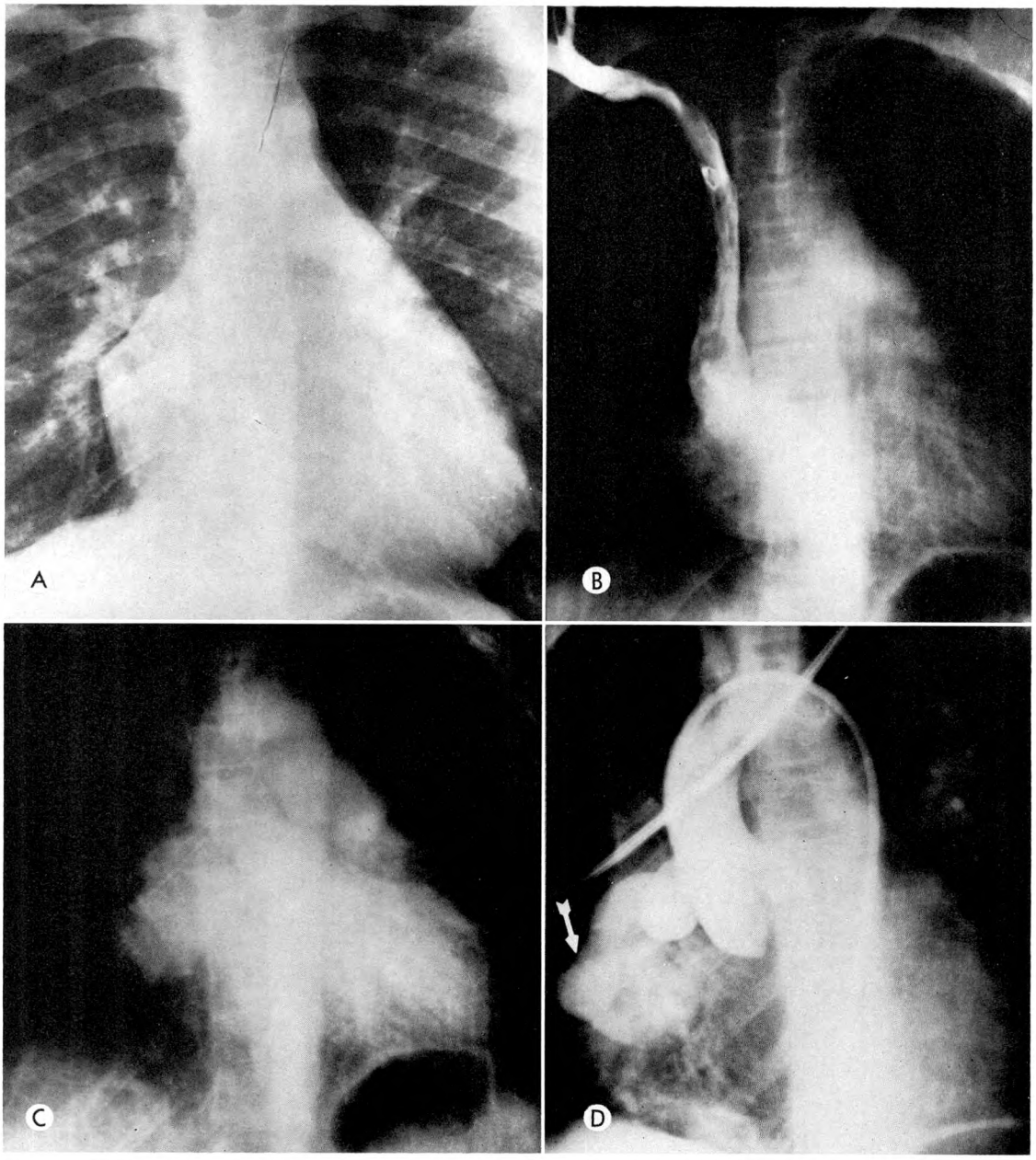


FIG. 5. Case VI. Congenital coronary arteriovenous fistula of the right coronary artery to right atrium. (*A*) Conventional teleroentgenogram showing enlargement of the right atrium, plethoric pulmonary circulation, and enlargement of the left ventricle in a 9 year old girl. (*B*) Intravenous angiocardiogram showing filling defects (jets) in the superior vena cava and right atrium with enlargement of the right atrium, ventricle, pulmonary artery, and branches. (*C*) When the left ventricle was visualized, there was reopacification of a large mass in the right atrium and reopacification of the pulmonary artery. (*D*) Retrograde aortogram dramatically demonstrates the aneurysmal right coronary artery flowing into the right atrium (arrow).

radical mastectomy (Case IX), (Fig. 8, *A* and *B*), laminectomy for a ruptured disk (Case X) (Fig. 9, *C* and *D*), right nephrectomy for kidney cancer (Case XI) (Fig. 10), and resection of the bowel (Case XII) (Fig. 11, *A* and *B*) resulted in traumatic arteriovenous fistulas in 4 cases. In the remaining 2, a gunshot wound of the left leg and a metallic fragment which lodged in the left arm (Fig. 12, *A* and *B*) were respectively responsible for traumatic arteriovenous fistulas.

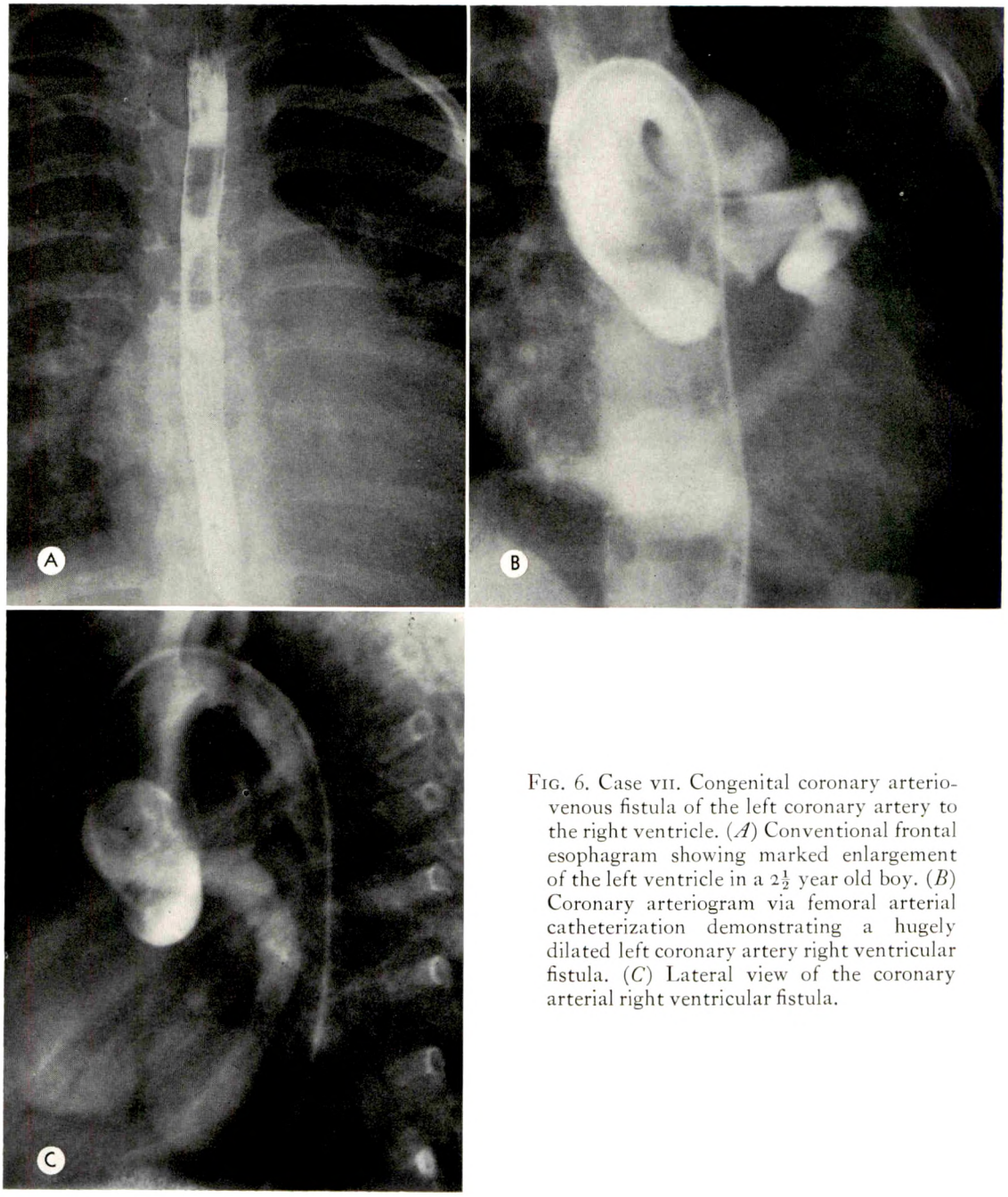


FIG. 6. Case VII. Congenital coronary arteriovenous fistula of the left coronary artery to the right ventricle. (*A*) Conventional frontal esophagram showing marked enlargement of the left ventricle in a $2\frac{1}{2}$ year old boy. (*B*) Coronary arteriogram via femoral arterial catheterization demonstrating a hugely dilated left coronary artery right ventricular fistula. (*C*) Lateral view of the coronary arterial right ventricular fistula.

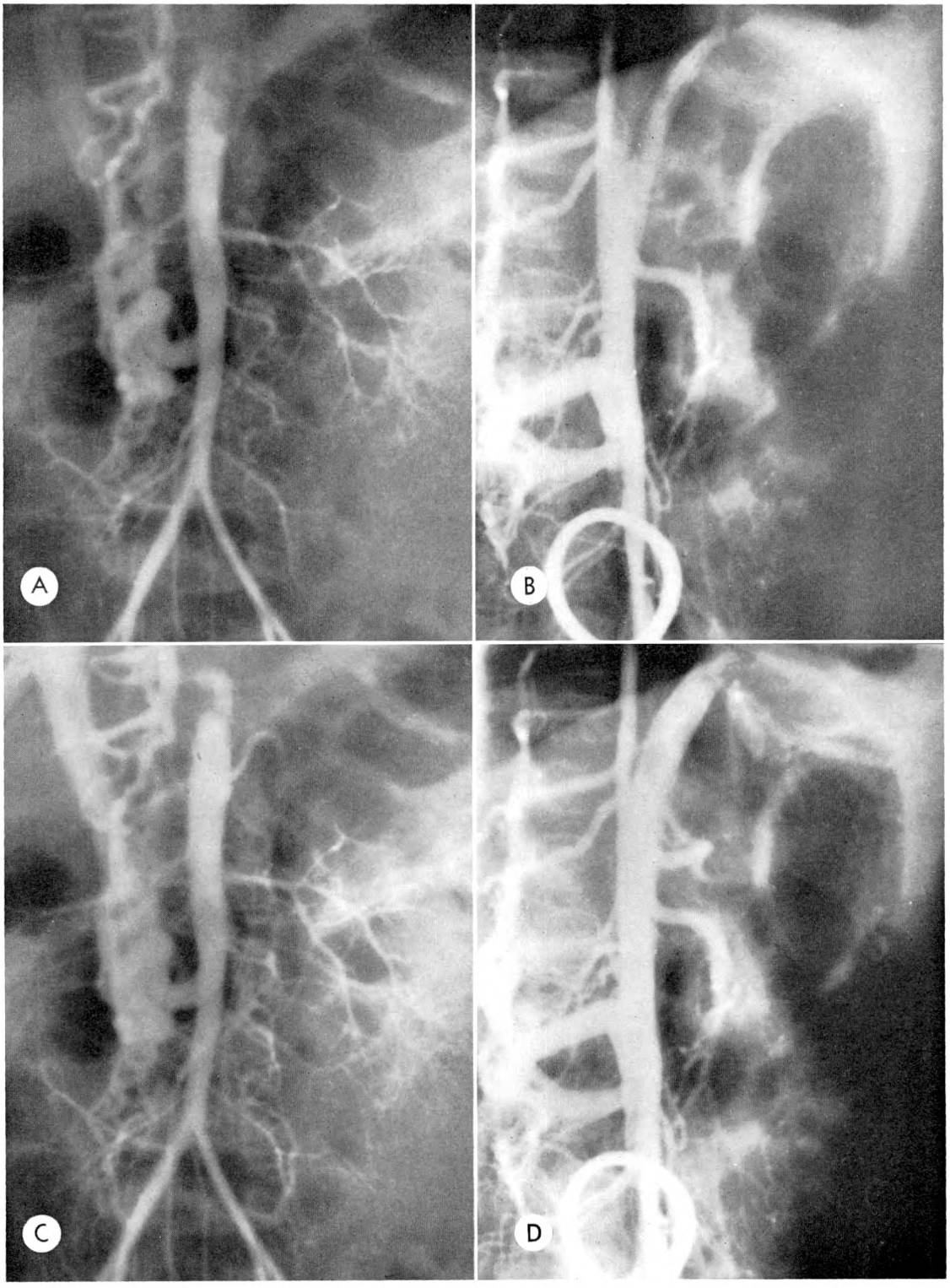


FIG. 7. Case VIII. Congenital arteriovenous lumbar fistula in a 5 month infant with Turner's syndrome. (*A*) Retrograde femoral aortogram showing the arteriovenous fistula in frontal view. (*B*) The biplane lateral view. (*C*) Frontal view one-half second later in the series. Note filling of ascending lumbar and azygos veins and inferior vena cava. (*D*) Biplane lateral view of *C*.

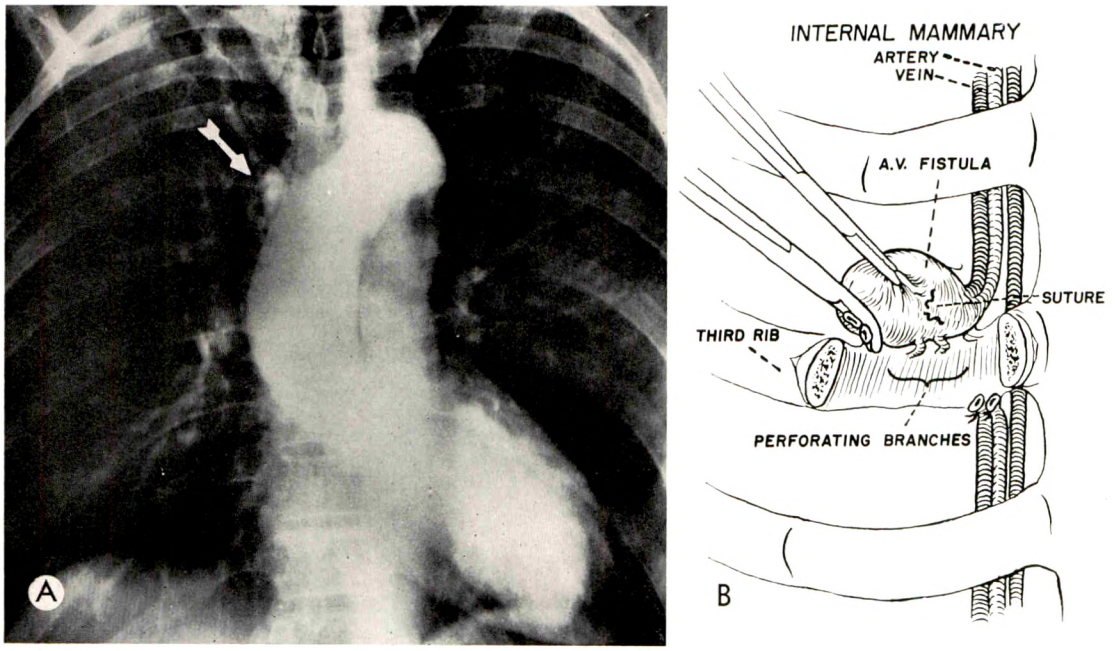


Fig. 8. Case ix. Postmastectomy right internal mammary arteriovenous fistula. (*A*) Frontal angiocardiogram showing the arteriovenous fistula (arrow). (*B*) Diagram of operative findings. (Reproduced with permission of the publisher.[7])

RESULTS

Selective catheterization of the involved artery, injection with dilute contrast agent and serial roentgenography of the arteriovenous fistula provided excellent visualization of the lesions in the majority of the patients (Case i, iii, vi, vii, viii, xi, xii and xiv) (Fig. 1, *A* and *B;* Fig. 3*B;* Fig. 5*D;* Fig. 6, *B* and *C;* Fig. 7, *A–D;* Fig. 10; Fig. 11, *A* and *B;* and Fig. 12, *A* and *B*). Intravenous angiocardiography was inferior to selective aortography for visualizing coronary arteriovenous fistulas (Fig. 5, *B* and *C*) but provided additional information regarding the right atrium, ventricle, and pulmonary arterial system. Satisfactory visualization of arteriovenous fistulas was secured with the intravenous method of aortography in Case ii, iii, iv, vii and ix (Fig. 2, *A* and *B;* Fig. 3*A;* Fig. 4, *A* and *B;* and Fig. 8*A*).[11] Despite this, selective arteriography would appear to be the method of choice for visualizing systemic arteriovenous fistulas.

DISCUSSION

The diagnosis and treatment of systemic arteriovenous fistulas are important; for, if the fistulas are large, serious hemodynamic consequences may result. For instance, Case x had severe heart failure which became refractive to digitalis therapy after an arteriovenous fistula had developed following a lumbar disk operation.[14] The heart failure promptly subsided after repair of the fistula (Fig. 9*E*). Similarly, ascites was present in a patient (Case xii) who developed a mesenteric arteriovenous fistula after bowel resection. Another patient (Case iii) had tachycardia, and high pulse pressures which were dramatically restored to normal after the eradication of the fistula.

The angiograms of Case i (Fig. 1, *A* and *B*) are of historic interest because they probably illustrate the first instance wherein serial roentgenography of such a lesion was secured.[1,2] Case x is also important because it was probably the first example of

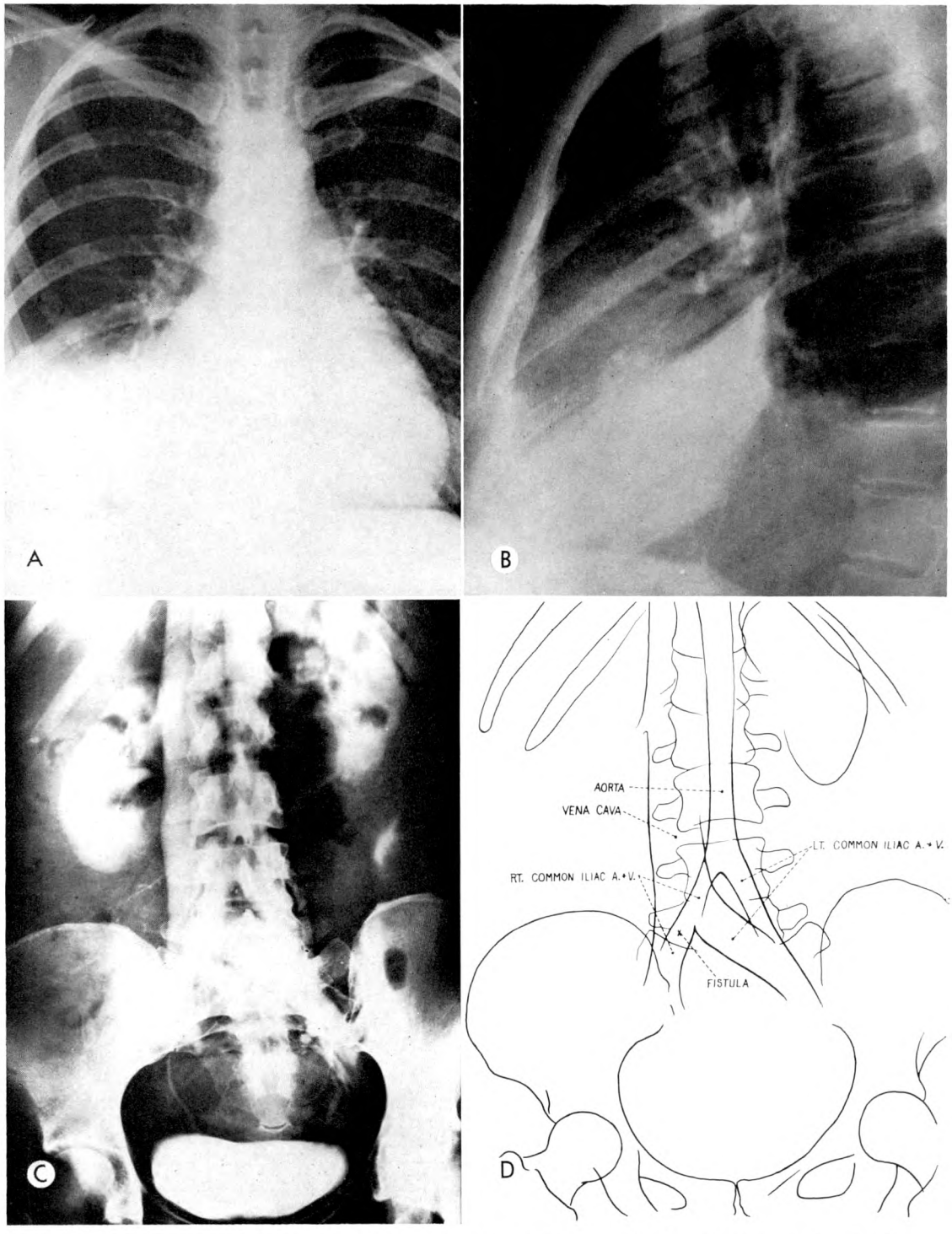


FIG. 9. Case x. Postlaminectomy (for herniated disk) arteriovenous fistula. (*A*) Conventional teleroentgenogram showing cardiac enlargement and fluid in the right pleural cavity. (*B*) Lateral view of the chest. (*C*) Intravenous abdominal aortogram showing the common iliac arterial inferior vena caval fistula. (*D*) Tracing of *C*.

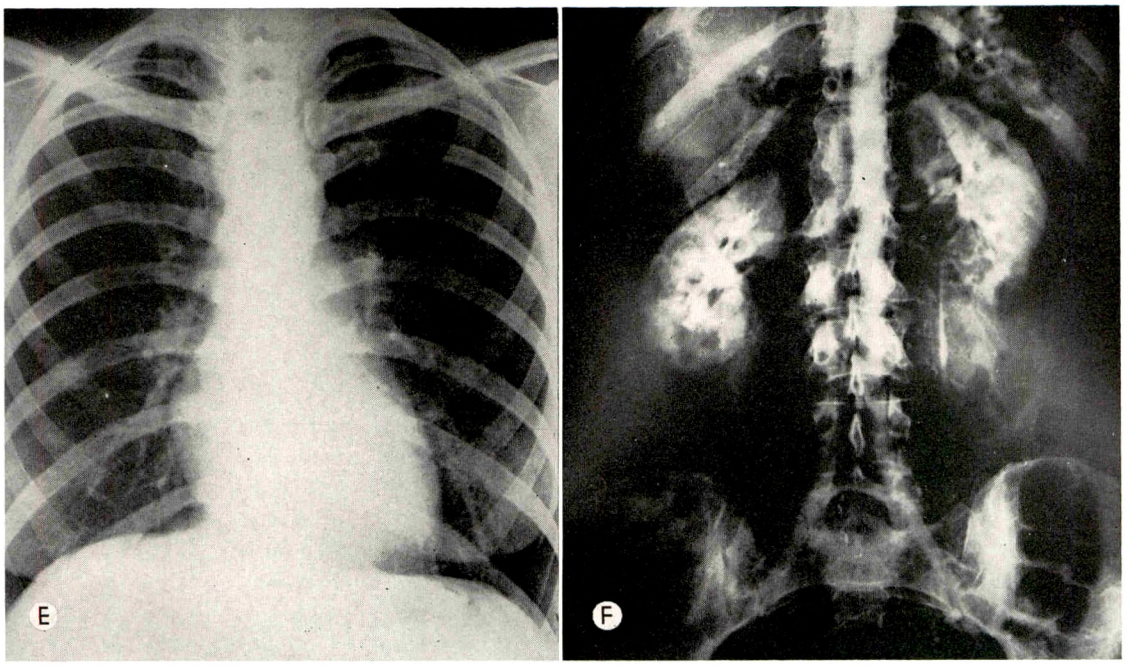


Fig. 9. Case x. (*E*) Postoperative normal chest. (*F*) Normal abdominal aortogram. (Reproduced with permission of the publisher.[14])

an iliac artery inferior vena caval fistula to be visualized by the simultaneous double intravenous method of abdominal aortography.[14] Similarly, the arteriovenous fistulas of Case II, IV, XII, and XIII were opacified by the method of abdominal aortography and peripheral arteriography.[11] It would appear, though, that coronary arteriovenous fistulas are better demonstrated by coronary arteriography (Fig. 5*D;* and 6, *B* and *C*);[4,6,10] however, intravenous angiocardiography provided additional data such as the size of the recipient chamber and associated areas of blood flow (Fig. 5, *B* and *C*). The arteriovenous fistula in Case II (Fig. 2, *A* and *B*) was visualized with bilateral simultaneous angiocardiography,[15] in Case III (Fig. 3*A*) it was demonstrated by intravenous carotid and verte-

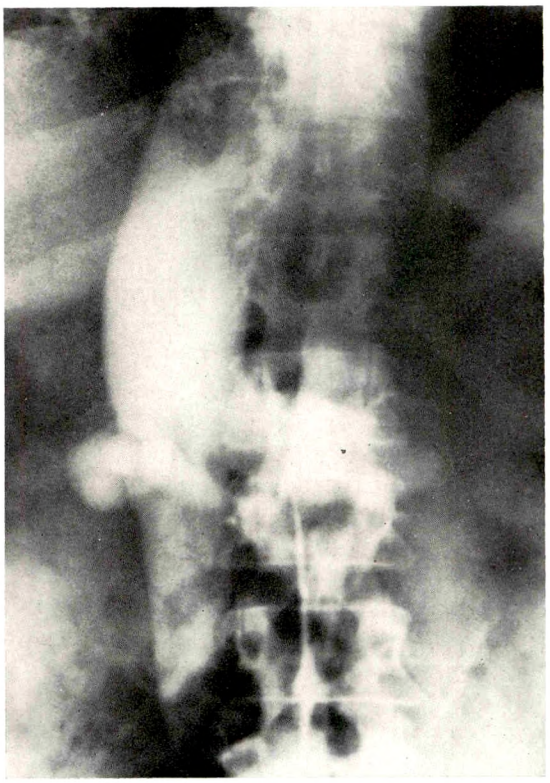


Fig. 10. Case XI. Percutaneous retrograde renal arteriogram showing an arteriovenous fistula between the right renal artery and inferior vena cava following nephrectomy for carcinoma of the kidney.

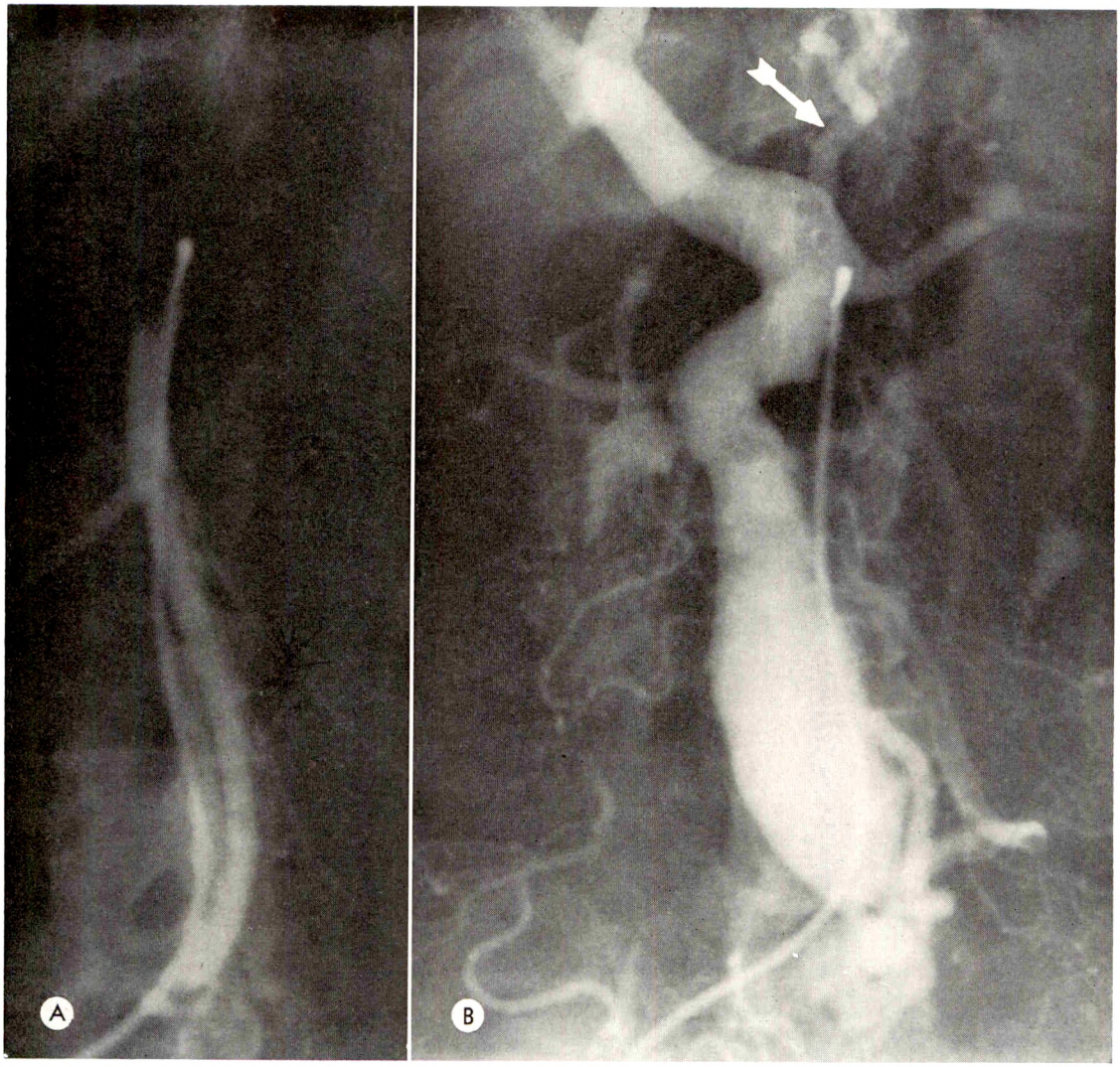


FIG. 11. Case XII. Mesenteric arteriovenous fistula following resection of gangrenous bowel. (*A*) Mesenteric arteriogram following percutaneous retrograde femoral catheterization. (*B*) The venous phase of the fistula showing the hugely dilated mesenteric and portal veins. Note, too, esophageal varicosities (arrow).



FIG. 12. Case XIV. Arteriovenous fistula of the left elbow resulting from a flying steel fragment. (*A*) Left brachial arteriogram. Arrow points to metallic fragment. (*B*) The arteriovenous fistula one-half second later in the series.

bral arteriography,[12] while in Case VI and IX (Fig. 5, *B* and *C;* and 8*A*) single injection intravenous angiocardiography sufficed.

SUMMARY AND CONCLUSIONS

Contrast roentgenography is essential for diagnosis and proper management of arteriovenous fistulas. In a series of 14 patients with systemic arteriovenous fistulas, the best results were obtained by selective catheterization or needle puncture of the involved artery, injection of dilute contrast medium, and serial roentgenography in order to secure maximal filling of the lesion. When intra-arterial puncture is inadvisable, either because of occlusive or aneurysmal disease, intravenous aortography may be used to establish the diagnosis; the roentgenograms, however, will not be as strikingly opacified as with the direct injection procedures.

Eight of 14 patients had congenital arteriovenous fistulas: right upper extremity, 2 cases; scalp and left leg, one each respectively; 3 patients had coronary arteriovenous fistulas; and a 5 month infant with Turner's syndrome had a lumbar arteriovenous fistula. Of the 6 patients with arteriovenous fistulas due to trauma, 4 followed operation: one patient had a right mammary arteriovenous fistula following mastectomy for cancer; another a right common iliac artery inferior vena caval fistula following laminectomy for ruptured disk; the third patient a renal artery inferior vena caval fistula 1 year following nephrectomy for carcinoma of the right kidney; and the last patient developed a



Fig. 13. Case IV. (*A*) Frontal photograph of the legs showing extensive ulceration and enlargement of the left limb. (*B*) Lateral photograph.

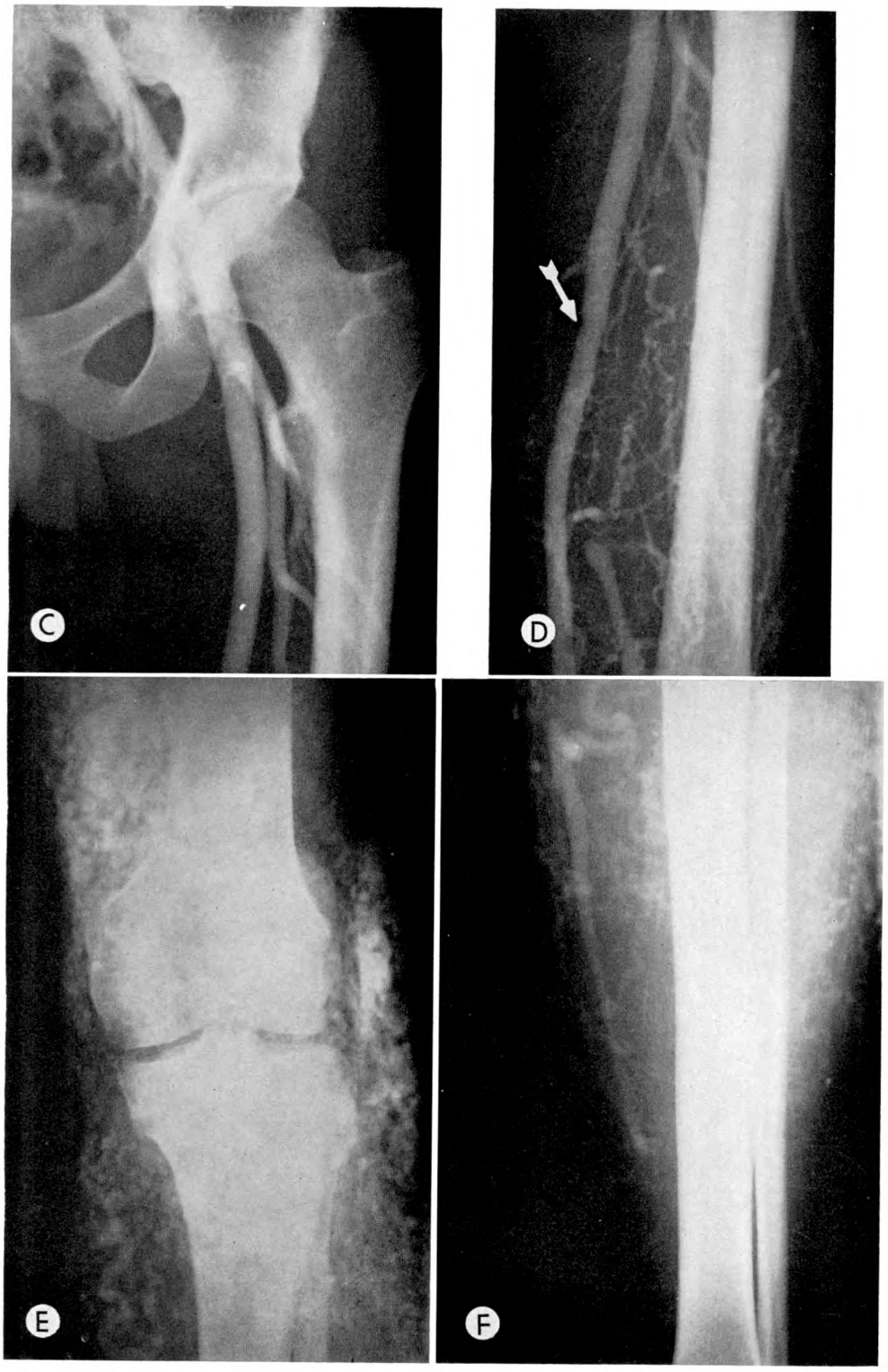


FIG. 13. Case IV. (*C*) Selective arteriogram showing enlargement of the common, superficial, and deep femoral arteries of the left leg. (*D*) Serial arteriogram of the arteriovenous channels in the upper thigh. Arrow points to the origin of the graft. (*E*) Serial arteriogram showing huge cirsoid arteriovenous communications. (*F*) The severe arteriovenous fistular changes of the lower leg are demonstrated.

mesenteric arteriovenous fistula after bowel resection. In 2 patients gunshot wounds and a flying steel chip from an ax were responsible for limb arteriovenous fistulas.

Operation was curative in every patient with a traumatic arteriovenous fistula and in 4 of the patients with congenital arteriovenous fistulas. In one patient with multiple arteriovenous fistulas of a leg, operation was palliative; amputation of the limb has, however, been recommended. Three patients with serious hemodynamic disturbances owing to systemic arteriovenous fistulas were restored to normal states, underscoring the importance of diagnosis and treatment.

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ADDENDUM

Since this paper was accepted for publication, Case IV (Table 1) was readmitted to The New York Hospital on September 6, 1962. In May, 1962, he had gone to a hospital in another state where the left leg had been incised, explored, and a synthetic superficial femoral arterial graft inserted. Following this, the ulcerations of the leg had increased (Fig. 13, *A* and *B*). Percutaneous right femoral catheterization and retrograde serial arteriography of the left leg on September 7, 1962 disclosed huge superficial and deep femoral arteries, but, now, with increased multiple arteriovenous fistulas of the lower thigh extending well below the knee (Fig. 13, *C*, *D*, *E* and *F*). A left mid-thigh amputation was done on September 13, 1962. Dissection of the specimen confirmed the angiocardiographic findings.

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ANEURYSM OF THE RENAL ARTERY

By SANTIAGO SANCHEZ CHECA* *and* BENIGNO SOTO RAMOS†
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ONE cause of abdominal hemorrhage is spontaneous rupture of arterial aneurysms of the different branches of the aorta.

Von Ronnen,[19] from a study of abdominal aneurysms in 88,772 autopsies, found that 0.01 per cent were related to the renal artery. Abeshouse,[1] in 1951, also concluded that renal aneurysms occurred more frequently than those of other arteries; he explained this on the basis of the development of more adequate auxiliary methods.

Until 1950 the majority of abdominal arterial aneurysms were diagnosed at postmortem examination. Sometimes their presence was suggested on plain roentgenograms of the abdomen. In this regard the work by von Ronnen is very important.

Abdominal aortography, as described by dos Santos[5] in 1929, could not be used for the study of renal aneurysms because of the numerous and dangerous complications. It was not until 1953 when Seldinger devised a safer method that roentgenographic confirmation of arterial aneurysms became possible. Since then reports about renal aneurysms have appeared more frequently.[2,6,15]

The diagnosis of renal aneurysms is more valuable when made at a preclinical stage. Generally, the first symptoms occur with rupture and this reduces the possibility of therapy. In other cases the patients present vague symptoms that can be attributed to other reasons, such as pain in the lumbar region. These points should be considered by the physician and appropriate studies should be ordered.

By selective angiographic study a correct diagnosis can be made. The condition of the kidneys, their functional status, the affected vessels and the existing complications can be demonstrated. This is valuable information for the surgeon.

It is the purpose of the present communication to call attention to this pathologic condition, the necessity of making an early diagnosis and the employment of selective angiography by which a definitive diagnosis of aneurysm can be made. The following is an illustrative case.

REPORT OF A CASE

P.H., a 72 year old male, was hospitalized because of persistent and profuse hematuria and pain in the left lumbar region. The clinical examination revealed an obese patient with tenderness localized in the left flank. The urine contained considerable blood.

Intravenous pyelograms showed absence of contrast medium in the left kidney and a round calcific density, 3 cm. in diameter, in the left renal hilar region. These findings were compatible with the presence of an aneurysm of the renal artery. Retrograde pyelograms revealed lateral and outward displacement of the upper portion of the ureter. The renal pelvis was not completely filled and it was round-shaped with a concavity toward the midline. Selective renal angiography was performed by femoral catheterization and disclosed that the renal artery was normal in caliber but displaced upward, describing an arch with the concavity downward. It was visualized in the hilus, the division of the renal artery into its superior, anterior medial and posterior medial branches (Fig. 1).

The inferior renal artery was not visualized and in its pathway was a 4×4 cm. sac, extending to the inferior pole of the kidney and displacing the other renal vessels upward and backward. Although filled with contrast material, its density was less than that of the renal artery. On angiograms obtained 3 and 5 seconds after the injection of the contrast medium, this image persisted along with some filling defects.

The patient was operated on and the roentgenographic findings were confirmed.

The pathologic study showed a small aneurysmal dilatation of the inferior pole renal artery and a 4×4 cm. calcified hematoma sur-

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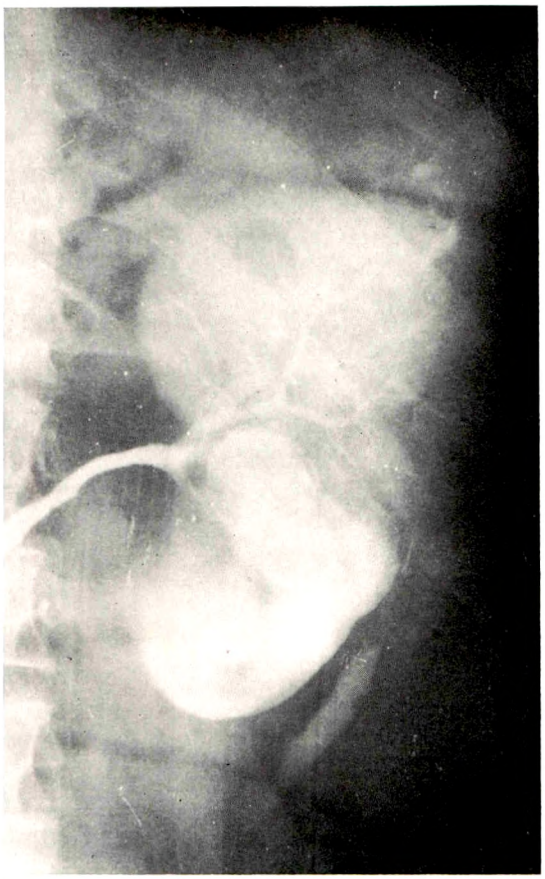


Fig. 1. Selective angiogram of the left renal artery shows a large aneurysm in the hilus of the kidney extending into the lower pole.

rounding the aneurysm, which was partially recanalized and formed a sac containing some blood clots. No endothelium was found in the wall of the sac (Fig. 2, *A* and *B*).

DISCUSSION

Clinically, the reported case was suggestive of a false aneurysm as described by Lowsley and Cannon;[12] however, because this is such a rare finding, it was not considered.

The plain roentgenogram of the abdomen showed the characteristic features which, according to the literature, are indicative of renal aneurysms. Selective renal angiograms clearly demonstrated the position of the aneurysm and its relation to the renal parenchyma as well as the circulation of the other portions of the kidney. These factors showed that the patient was a suitable subject for surgical treatment.

The clinical history did not reveal any symptoms that could be attributed to an

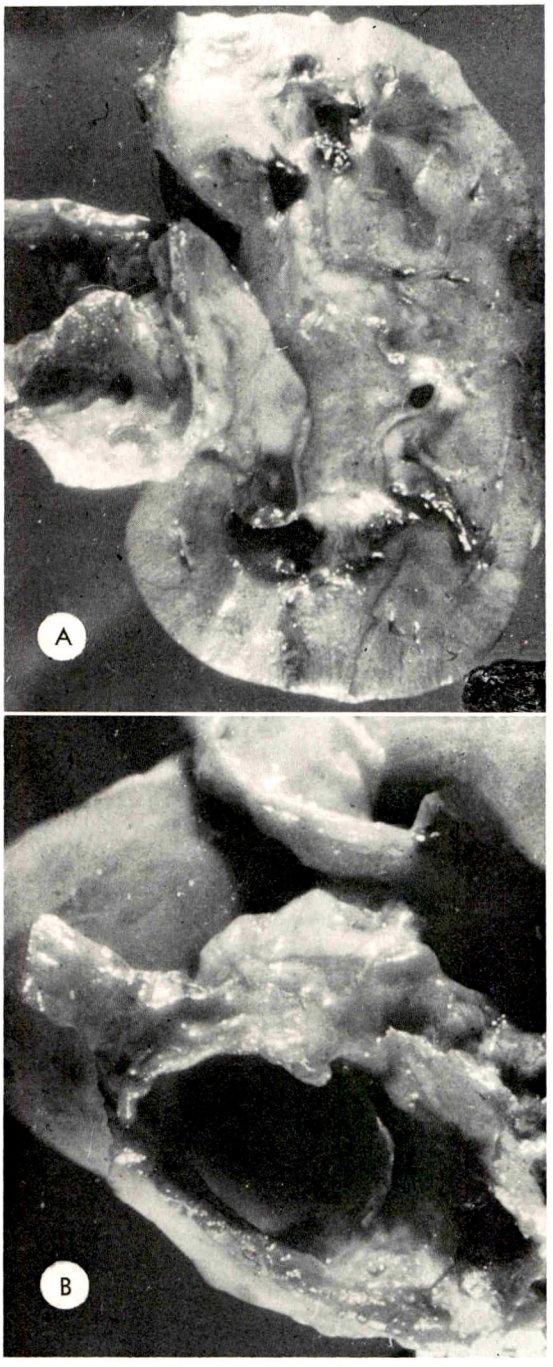


Fig. 2. (*A* and *B*) Anatomic specimen shows the site of the aneurysm to be the same as revealed by renal angiography.

aneurysm. The first manifestation was the persistent hematuria, which, according to the literature, indicates a false aneurysm. The case illustrates that it is possible for an aneurysm to be present without specific symptoms.

Renal angiography in these cases is of great value, enabling a positive diagnosis and the determination of a proper surgical approach. Ten years ago the procedure was not without risk; however, since 1953, the aortography technique has been improved to the point where it now can be considered a safe method offering many possibilities. It appears that selective renal aortography should be performed more often since similar cases have not been described in the Latin American literature and it can be assumed that percentage wise the incidence is similar to that reported in other countries.

SUMMARY

A case of primary renal aneurysm complicated by a secondary hematoma has been presented. The lesion was suspected after a study of the plain roentgenograms of the abdomen; however, a definitive diagnosis was reached only after selective renal angiography was performed. This revealed the secondary complication, the localization of the aneurysm and the functional status of the kidneys.

The advantages of selective renal angiography and its safety are stressed.

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INTRACAVERNOUS ANEURYSMS OF THE INTERNAL CAROTID ARTERY*

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THE behavior of aneurysms arising from the internal carotid artery as it traverses the cavernous sinus is unlike that of aneurysms arising elsewhere in the skull. Their rupture because of their location gives rise to a caroticocavernous fistula instead of the usual subarachnoid hemorrhage. The intimate relationship between the third, fourth, fifth and sixth cranial nerves and the aneurysms explains to an extent, but not entirely, the cavernous sinus syndrome described in the literature by Bartholow[1] in 1872 and later by McKinney *et al.*[4] and Jefferson.[2] As a rule, the dural lining of the cavernous sinus protects the patients from fatal accidents, although an eye is apt to be lost.[5] The dura, however, does not prevent the marked development of these aneurysms which because of their relationship with the base of the skull very often produce osseous changes.

The purpose of this paper is to report our findings in 24 cases of intracavernous aneurysms seen at the Neurological Institute of Milan. These represent 11 per cent of a consecutive series of 209 cases of cerebral aneurysms which we have observed from January, 1946 to December, 1961. Rischbieth and Bull,[6] and Krayenbühl and Yasargil[3] found in their series that of cerebral aneurysms, the incidence of intracavernous lesions was 5 and 6 per cent, respectively.

CLINICAL FINDINGS

The distribution according to age of our 24 patients, whose ages ranged from 22 to 71 years, is shown in Table I. The greatest number of cases was found to be in the fifth and sixth decade.

In agreement with the data reported in the literature,[2,5,6] females (17 cases) were noted to be affected more often than males (7 cases). Thirteeen of the aneurysms were situated on the left side and 11 on the right. Many patients showed marked evidence of arteriosclerosis and an elevated diastolic pressure (Table II), which in 12 cases was 100 mm. Hg or more. The systolic pressure exceeded 160 mm. Hg in 9 patients.

The onset of neurologic symptoms and signs was slow in 11 cases, sudden in another 11 and in 2 cases, which were accidently discovered (Case 13 and 17), no symptoms were present.

The classic cavernous sinus syndrome is characterized by the onset of pain in the area of one or more of the trigeminal nerve branches, accompanied or followed by palsy of one or more of the oculomotor nerves and by a trigeminal nerve sensory loss. Pain in and around the eye and face was the most frequent symptom in our group, being present in 22 cases. As observed by Meadows,[5] it tended to occur in bouts, leaving the patient free or relatively free in the interval. Palsy of the oculomotor nerves, either accompanying the

TABLE I

AGE INCIDENCE OF PATIENTS WITH CAVERNOUS SINUS ANEURYSMS

Decade	20–30	30–40	40–50	50–60	60–70	70 and Over
No. of Cases	2	3	6	9	3	1

* From the Departments of Radiology and Neurosurgery, Istituto Neurologico, Milano, Italy.

TABLE II

SUMMARY OF CASES STUDIED

Case No.	Sex	Age	Side	Osseous Changes	Calcification	Angiography	Mode of Onset	Duration of Symptoms	Cranial Nerve Involvement (chronologically listed)	Blood Pressure	Treatment	Result and Observations
1	F	45	L	+	−	−	slow	1 mo.	II	170/100		Death from spontaneous hemorrhage. Autopsy performed
2	M	22	R	+	+	−	slow	2 yr.	V (1, 2)	140/80	Transfrontal exploration. Internal carotid ligation	Improvement
3	F	48	R	−	−	+	sudden	6 mo.	III IV VI V (1, 2, 3) I	150/90		
4	F	58	R	+	+	−	slow	1 yr.	II III (partial)	165/100	Transfrontal exploration	Death from hemorrhage during operation
5	F	60	R	+	+	+	slow	2 yr.	III IV VI II	190/110		
6	M	40	R	+	−	+	sudden	1 mo.	III IV VI	110/70	Internal carotid ligation and intracranial trapping	No change
7	F	27	L	−	+	+	sudden	3 yr.	V (1, 2, 3)	125/70		
8	F	59	L	+	+	+	slow	5 yr.	VI II V (1, 2, 3) IV III (partial)	185/110		
9	F	53	L	+	−	+	slow	1 yr.	I II	180/105	Transfrontal exploration. Common carotid ligation	Lack of filling of the aneurysm. No change after ligation
10	F	65	L	−	−	+	sudden	15 da.	III	170/95		
11	F	42	L	+	+	+	slow	6 mo.	II VI III V (1, 2 and motor)	125/80	Internal carotid ligation	Improvement
12	F	37	L	+	−	+	sudden	20 yr.	II III	130/70	Common carotid ligation	Improvement
13	M	38	L	−	−	+	—	—	—	110/60		Temporal arteriovenous angioma on right. Small asymptomatic aneurysm on left
14	F	47	L	+	−	+	slow	2 yr.	III V (1, 2, 3)	210/110	Internal carotid ligation	Improvement
15	M	57	R	+	−	+	slow	1 mo.	II III IV VI V (1, 2, 3)	185/110	Common and internal carotid ligation	No change
16	F	71	L	+	+	+	sudden	3 yr.	III IV VI	170/80		Primitive trigeminal artery. Death from arteriography
17	F	54	R	−	−	+	—	—	—	165/100		Small, asymptomatic aneurysm
18	F	52	L	+	−	+	sudden	1 yr.	III IV VI V (1)	140/80		
19	F	56	R	+	−	+	slow	1 yr.	III IV VI II	155/95		
20	M	47	R	+	−	+	slow	6 yr.	III V (1)	165/90	Internal carotid ligation	Death from carotid ligation
21	M	34	L	+	−	+	sudden	3 da.	III IV VI	150/100		Injury followed by arteriovenous fistula of 2 weeks' duration
22	M	60	R	+	+	−	sudden	33 yr.	III IV VI II	140/90		
23	F	53	L	+	−	+	slow	4 mo.	III IV VI V (1)	140/95	Common carotid ligation	No change
24	F	57	R	+	−	+	sudden	2 mo.	III IV VI V (1, 2, 3)	150/90	Internal carotid ligation	Improvement

pain or following it, appeared next in frequency (Table II). This occurred in 17 cases: total ophthalmoplegia in 11, isolated palsy of the third nerve in 5, and palsy of the third and sixth nerve in one case. Eleven patients complained of a trigeminal nerve sensory loss of one or more branches, and in one case there was involvement of the motor root.

The initial clinical symptom in 5 patients was a slowly progressing visual failure which in one case (Case 1), possibly because of the sudden and early death of the patient, was the only presenting feature. A similar case was reported by Meadows.[5] The other 4 patients had involvement of one or more of the nerves crossing the cavernous sinus. One patient (Case 9) with an aneurysm with suprasellar expansion had first a loss of smell, followed by visual failure, and then a bitemporal defect of the visual fields. Another patient (Case 8) also complained of bilateral inferior temporal quadrantanopsia. Exophthalmos was present in 3 cases and a cephalic murmur was noted in another 3. Jefferson[2] feels that there are 3 varieties of the cavernous sinus syndrome, based on the trigeminal root involved and on the site of the aneurysm. These are: the anterior variety, in which the first trigeminal branch is involved; the middle variety, in which the first and the second branches are involved; and the posterior variety, in which the 3 sensory branches and, although very rarely, the motor root are involved. According to this classification, 3 of our cases can be considered as being of the anterior variety, 2 of the middle and 6 of the posterior variety.

ROENTGEN FINDINGS

Roentgenologically, osseous changes were present in 19 or 80 per cent of our 24 cases.

PARASELLAR AND SELLAR LESIONS

Sosman and Vogt[10] stated in 1926 that "the erosion due to these pulsating sacs is also fairly characteristic in appearance. It involves or may involve one anterior clinoid, the lateral half of the body of the sphenoid on the same side, and a similar portion of the posterior clinoid." In our series, the most frequent and characteristic of these changes were elevation and erosion or destruction of the anterior clinoid, which we observed in 16 cases (67 per cent). The dorsum sellae, the posterior clinoids (10 cases), and the floor of the sella turcica (8 cases) were frequently decalcified and/or eroded.

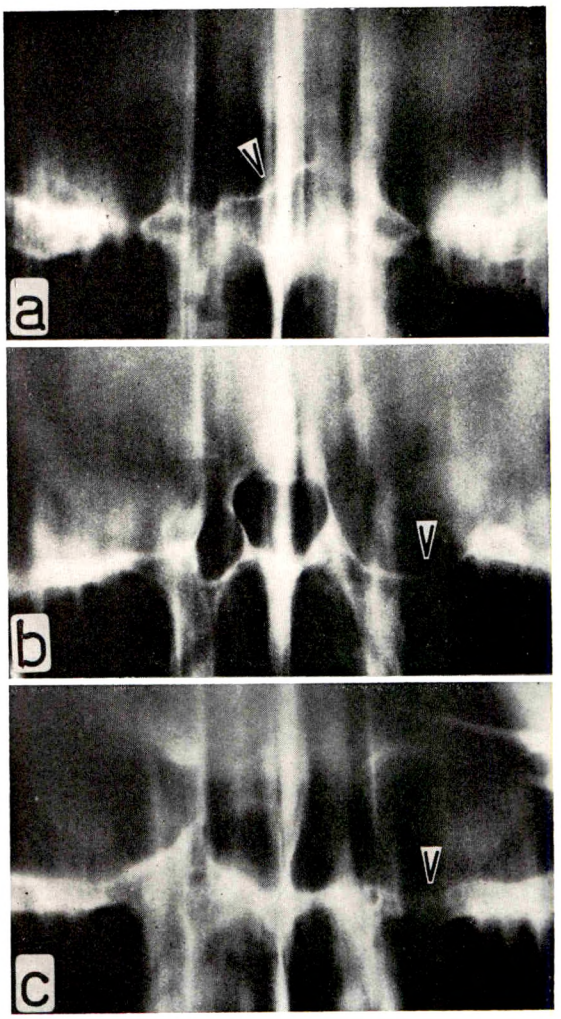


Fig. 1. Laminagrams of intracavernous aneurysms showing: (*a*) parasellar involvement, (*b*) erosion and (*c*) decalcification of the middle fossa.

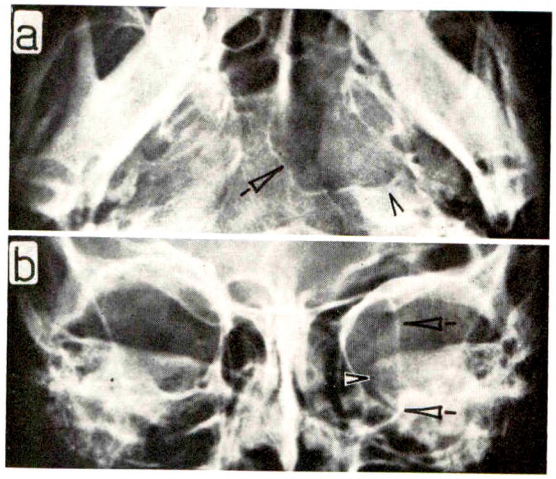


FIG. 2. (*a* and *b*) Case 12. Left intracavernous aneurysm. Erosion of the tip of the petrous pyramid (∧) and enlargement (Δ) of the superior orbital fissure are visualized. Erosion of the middle fossa is outlined by a thickened contour.

MIDDLE CRANIAL FOSSA

In the literature no particular mention is made of changes occurring in the middle cranial fossa; however, we were able to visualize such changes by laminagraphy. In 7 out of 10 cases, these studies showed a localized rounded erosion or, more frequently, thinning and decalcification of the base (Fig. 1, *a*, *b* and *c*). In 3 patients with very large aneurysms, the middle fossa was seen, in the basal view roentgenograms, to be definitely eroded. At times, the bony defect may show a thickened outline (Fig. 2, *a* and *b*).

SUPERIOR ORBITAL FISSURE

This is believed to be enlarged because of progressive erosion of the lesser and greater wings of the sphenoid. This was first described by McKinney, Acree and Stoltz[4] and later by Jefferson.[2] Enlargement of the superior orbital fissure was found in 15 cases of our series (62 per cent). Although Rischbieth and Bull[6] observed this in 74 per cent of their 23 cases of intracavernous aneurysms, they pointed out the frequency of asymmetry of the superior orbital fissure found in normal patients and felt that no standard measurement can be used for normal and pathologic states. Furthermore, they noted the same osseous changes in 4.7 per cent of the pituitary tumor cases (with or without the cavernous sinus syndrome), in 4 per cent of pterional, sphenoid wing and middle fossa meningiomas (generally associated with other roentgenographic changes), in approximately 20 per cent of orbital tumors and in one case of chordoma.

OPTIC CANAL

Special roentgenographic views for visualization of the optic canal were employed in 11 cases. The optic canal was normal in 3 cases, while in 6 its lower edge was clearly decalcified and in the remaining 2, as a result of destruction of the intervening bar, it communicated directly with the superior orbital fissure which was also partially destroyed. On the basis of our experience, we agree with Rischbieth and Bull[6] who consider this sign a common but not a pathognomonic finding in cases of intracavernous aneurysms. To the pathologic conditions reported by Rischbieth and Bull[6] which may produce erosion of the superior orbital fissure with or without communication with the optic canal, we are able to add mucocele of the sphenoid sinus and extradural angiofibroma of the middle fossa (Fig. 3, *a*, *b* and *c*).

PETROUS PYRAMIDS

The tips of the petrous pyramids were noted to be eroded in 2 cases of extremely large aneurysms (Fig. 1, *a*, *b* and *c*).

CALCIFICATIONS

Calcification of some type was present in 8 of our patients (33 per cent) and almost always was associated with some change in the surrounding bone. In 3 cases the curved linear shadow outlined the aneurysm almost completely (Fig. 4, *a*, *b* and *c*). In 5 cases, the wall was only partially calcified and at times appeared to be interrupted at several points. Rischbieth and Bull[6] observed calcification in 8 of their 23 cases (38 per cent) and Meadows[5] in 8 of his 15 cases (53 per cent).

Since the deposition of calcium is a

rather slow process, its roentgenologic demonstration depends mainly on the stage of the aneurysm when it is first seen. Calcifications are absent or very rare in cases with a short history. Meadows[5] reports it as a late finding in 5 of 15 patients studied; in some cases it was noted from 4 to 7 years after the onset of symptoms. In our opinion, the finding of an aneurysm completely outlined by calcification, or almost so, with a cavernous sinus syndrome should be considered pathognomonic. Calcifications are much more difficult to evaluate when they are limited in extension. Diffuse calcifications in tortuous arteries of arteriosclerotic patients may, at times, be interpreted erroneously as an aneurysm (Fig. 5).

DISCUSSION

Carotid angiography was performed in 20 cases in our series. In the remaining patients the diagnosis was made at autopsy (Case 1), at the time of operation (Case 2 and 4), and in one patient, the history, clinical symptoms, the visualization of a calcified ring shadow on one side of the sella turcica

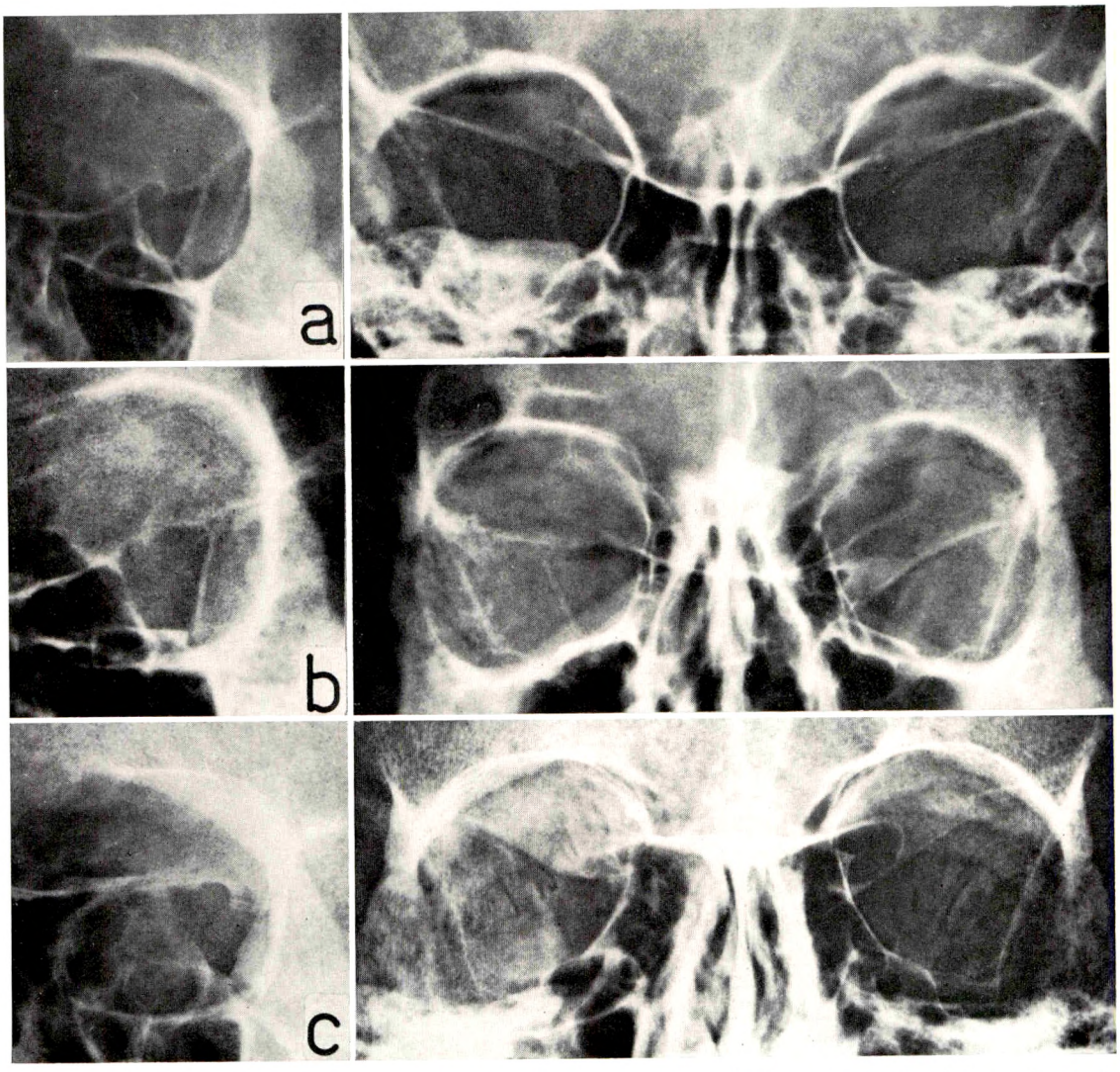


Fig. 3. Widening of the superior orbital fissure and erosion of the inferolateral margin of the optic canal: (*a*) intracavernous aneurysm, (*b*) extradural angiofibroma of the middle fossa and (*c*) sphenoidal mucocele.

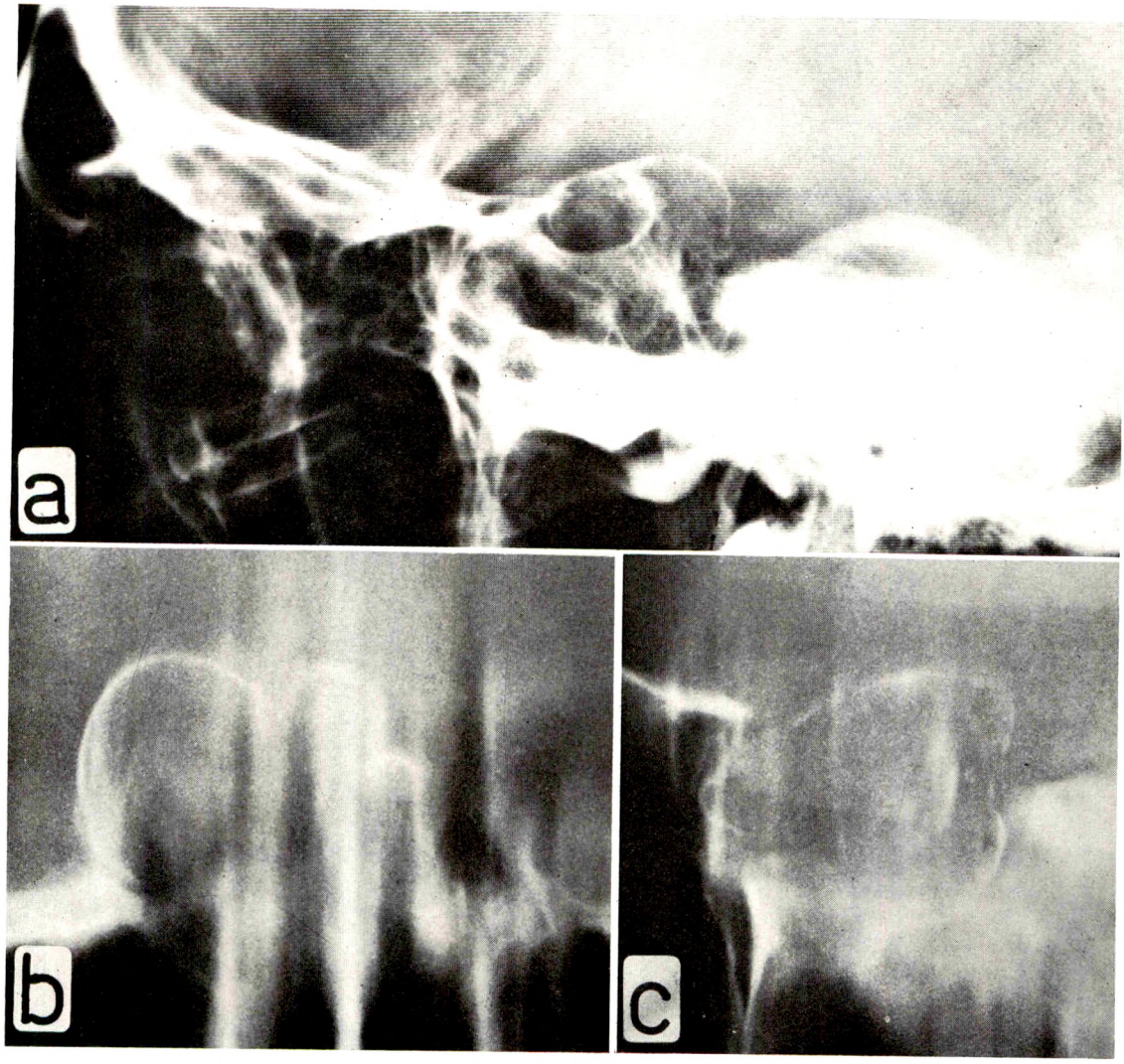


FIG. 4. (*a*) Case 22. On a plain roentgenogram the wall of the aneurysm is completely outlined by calcium. (*b* and *c*) Laminagrams also show the calcium deposition.

and the general condition of the patient made angiography unnecessary (Case 22, Fig. 4, *a*, *b* and *c*).

Cerebral angiography does not always reveal an existing intracavernous aneurysm. This was true in one of our cases (Case 9) in which the aneurysm was obscured by blood clots.

Very small asymptomatic aneurysms were discovered accidentally in 2 patients being studied for the possible presence of other lesions (Case 13 and 17, Fig. 6, *a* and *b*). These small saccular formations should not be confused with infundibular widening of the posterior communicating artery, as described by Saltzman[7] because of their intracavernous location. One of these patients (Case 13) presented a temporal arteriovenous angioma on the opposite side. This association is interesting as it brings some light on the formation of aneurysms. These malformations originate from weak points of the arterial wall which, as evidenced by histologic studies, are localized at the level of the bifurcations or insertions of an embryonal vessel. The latter type of aneurysm was present in one of our patients (Case 16), associated with

a primitive trigeminal artery (Fig. 6 *c*). It is felt that arteriosclerosis and hypertension are not so much causative factors but rather factors favoring the slow development of aneurysms and an explana-

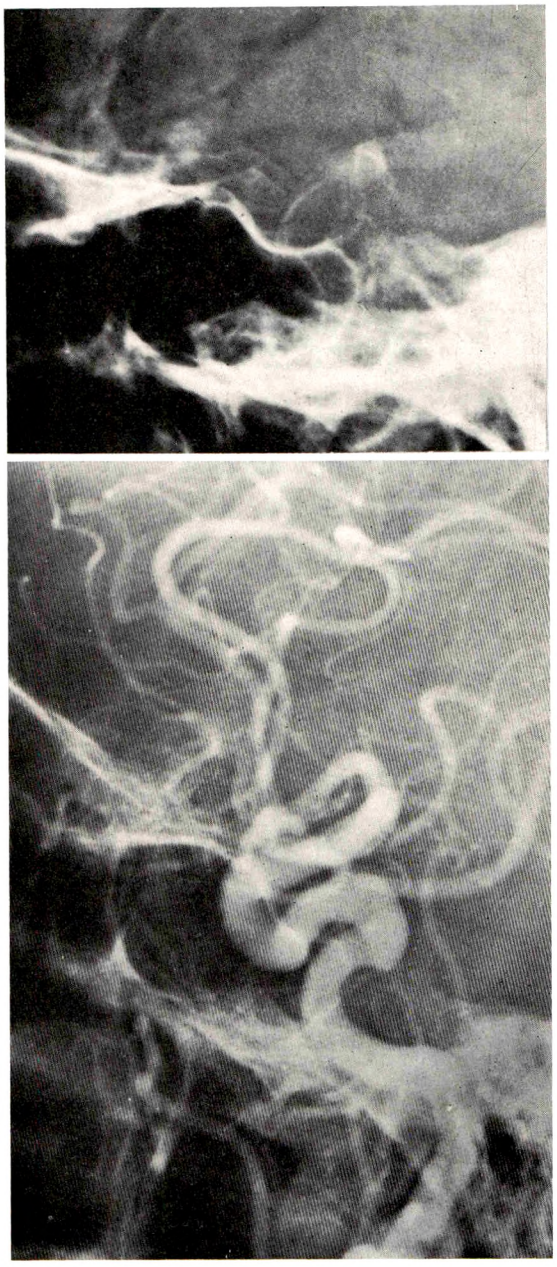


Fig. 5. Large rim of calcification in a patient presenting symptoms related to trigeminal involvement. An intracavernous aneurysm is suspected but only arteriosclerotic changes are demonstrated on cerebral angiography.

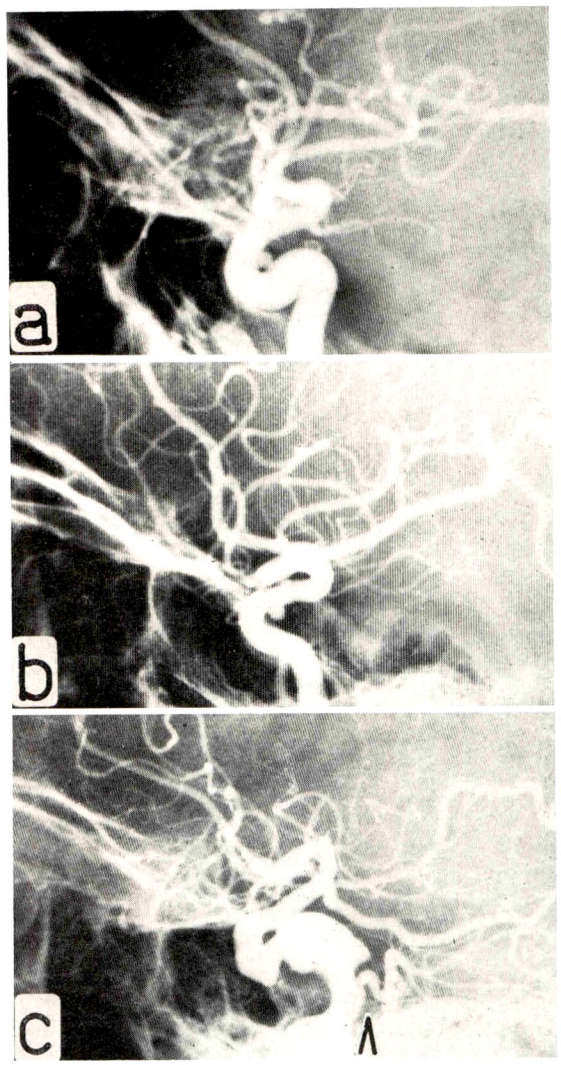


Fig. 6. (*a* and *b*) Case 13 and 17. Two very small, asymptomatic intracavernous aneurysms. (*c*) Case 16. Aneurysm associated with a primitive trigeminal artery (∧).

tion for the late clinical manifestations. In one patient (Case 21), the symptoms appeared after trauma to the skull, followed by a caroticocavernous fistula. The case is included in the present series since subsequent cerebral angiography, performed 2 weeks after the first, demonstrated the absence of the fistula and the presence of an aneurysm.

Schiefer and Marguth[8] have described intrasellar aneurysms (Fig. 7, *a* and *b*) and defined their clinical pattern. Two of

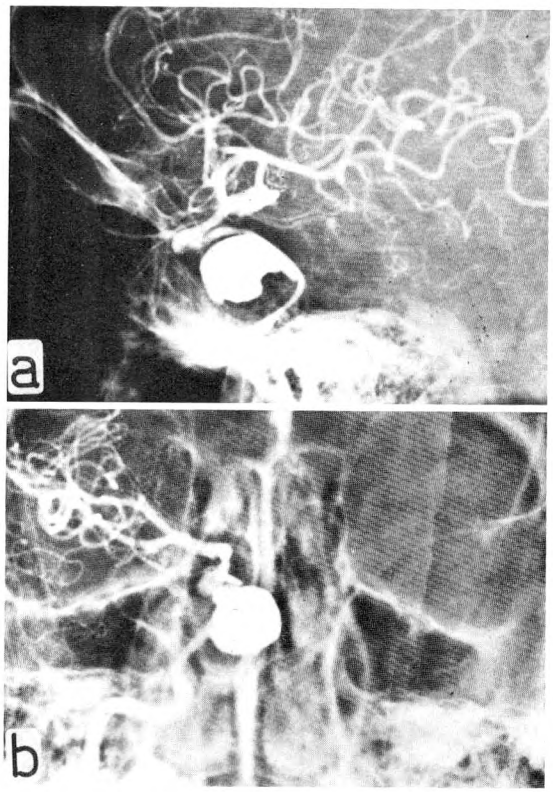


FIG. 7. (*a* and *b*) Case 19. Intrasellar aneurysm. Tumor-like compression and distortion of the infraclinoid segment of the internal carotid artery.

our case studies (Case 9 and 19) fit into this group. In another patient (Case 12), the sella turcica was only partially invaded.

Very large aneurysms with internal diameters averaging 4 cm. were found in 4 patients. Such lesions are similar to tumors in that they displace adjacent anatomic structures and also large vessels (Fig. 8, *a* and *b*).

On angiograms some aneurysms appear to be small although in reality they are quite large. This is due to the considerable amount of clotting in the cavity. In 4 cases, the aneurysm showed an uncommon finger-like appearance with lateral expansion into the middle fossa (Fig. 9, *a*, *b* and *c*). Usually, the internal carotid artery maintains its normal appearance and course even in the presence of large aneurysms; however, in our Case 19 the intracavernous portion of the cerebral artery was distorted and its lumen narrowed (Fig. 7, *a* and *b*).

At least 3 cases (Case 4, 9 and 11) belong to the group defined by White and Adams[12] as "combined supra- and infraclinoid aneurysms of the internal carotid artery." In these cases the aneurysm expands mainly in its intracavernous portion and continues into the supraclinoid portion of the internal carotid artery as a fusiform dilatation (Fig. 10). The cavernous sinus syndrome is complicated in such cases by visual changes due to compression of the optic nerve; monocular blindness can occur.[12]

Bilateral intracavernous aneurysms are not included in our series. Seltzer and Hurteau[9] described 10 such cases, one of their own. These were revealed by angiographic studies in only 3 instances; in the others, bilateral localization of the aneurysm was ascertained at necropsy.

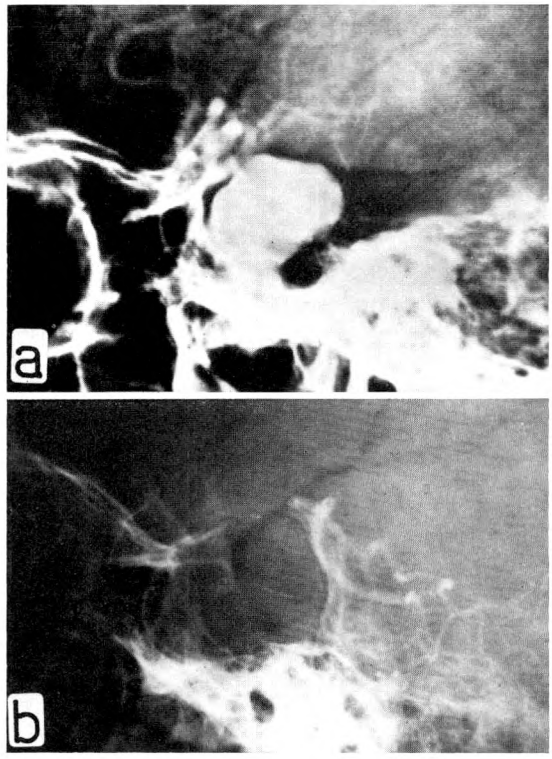


FIG. 8. (*a* and *b*) Case 23. Large intracavernous aneurysm displacing and distorting the basilar artery. Anterior to this artery are a few calcified deposits.

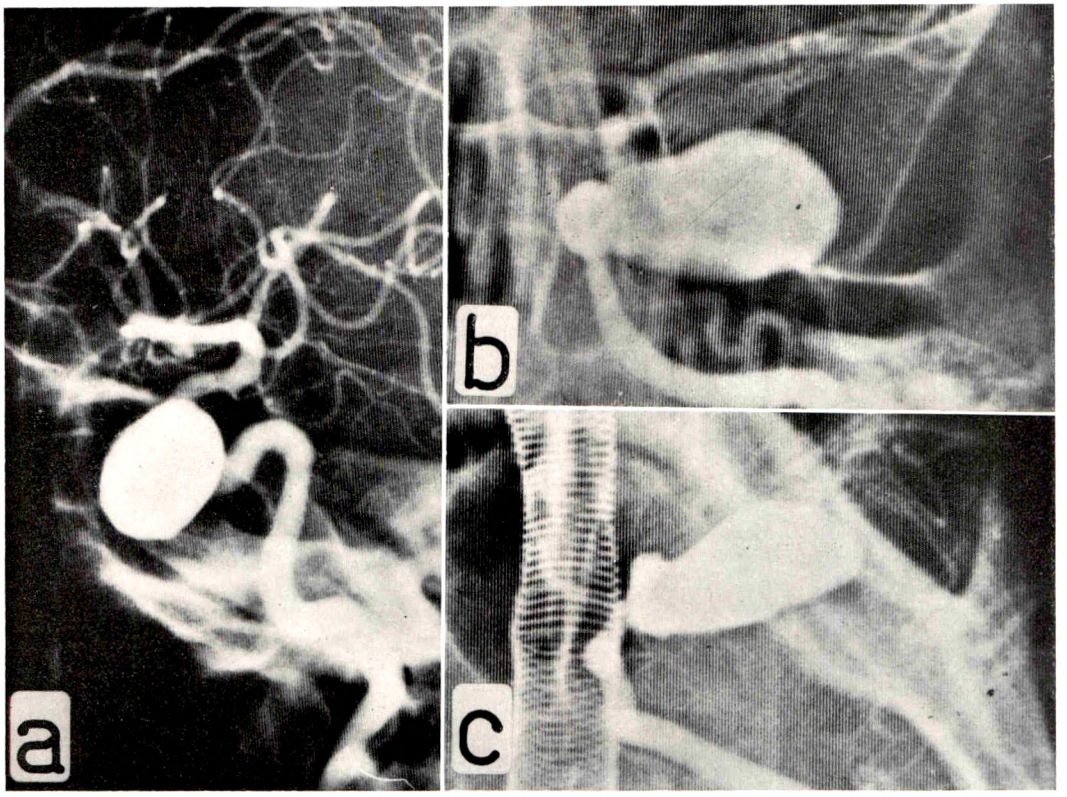


Fig. 9. (*a*, *b* and *c*) Case 18. Finger-like appearance of an intracavernous aneurysm in (*a*) lateral, (*b*) anteroposterior and (*c*) basal view.

According to Tönnis and Schiefer,[11] the ophthalmic artery is opacified in 73 per cent of the normal cases, and Yasargil[13] found this to be true in 98 per cent of his cases. This artery was demonstrated on angiograms in only 11 of our 20 cases of intracavernous aneurysms (55 per cent).

Intracranial circulation was involved in 3 patients with very large aneurysms and caused poor visualization of only a few arteries. Vasal spasm, which is frequently noted in other intracranial aneurysms, especially near the aneurysmal sac, was observed only once by us (Case 16). In this patient, a 71 year old female, hemiplegia and death occurred immediately after angiography.

TREATMENT

Two of our patients, who were seen before cerebral angiography became an accepted technique, and one in whom an aneurysm was not revealed by angiography underwent chiasmatic exploration. One of these patients died from hemorrhage during the operation (Case 4) and the other 2 had subsequent ligation of the carotid artery (Case 2 and 9). Ligation was also done in 8 additional patients. The common carotid artery was ligated in 3 and in one case the common carotid artery and then the internal carotid artery were ligated. In 5 patients the internal carotid artery was ligated at the neck and in the tenth case ligation was carried out at the neck and intracranially, before the branching off of the ophthalmic artery.

Ligation was always preceded by tests so as to determine the existence of a sufficient cross flow and also patients were adequately prepared with progressive digital compression of the carotid artery. However, in one case (Case 20), the operation was followed by hemiplegia and death.

Clinically, 5 of the patients having ligation showed partial improvement and in the remaining 4 no change was noted. The progression of these aneurysms is extremely slow with periods of partial remission of the clinical symptomatology; nevertheless, ligation of the carotid artery is indicated in selected cases as it limits further development of the aneurysm and may attenuate the existing damage. Eleven cases were not operated on: in 6 the age, absence of a satisfactory collateral circulation and/or the general condition of the patient did not warrant ligation; 3 patients refused the proposed intervention and in the remaining 2 cases surgical procedure was deemed unnecessary because of the lack of symptoms.

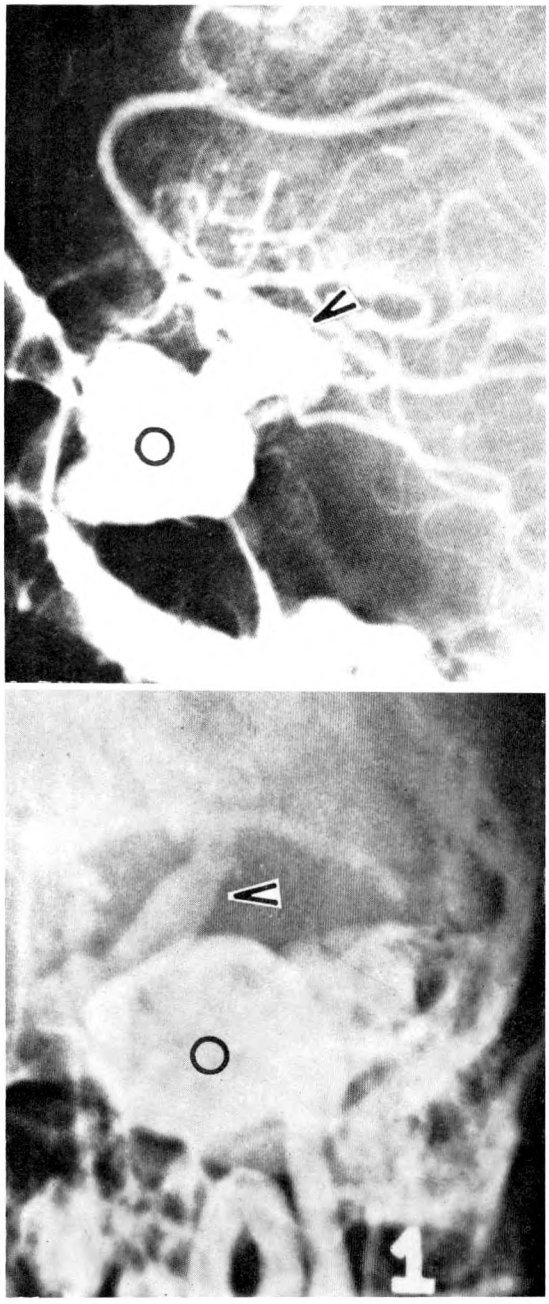


FIG. 10. Case 11. Combined supraclinoid and infraclinoid aneurysm. Intracavernous portion (○) and supraclinoid fusiform dilatation of the internal carotid (∧) are evident.

SUMMARY

Aneurysms of the cavernous sinus have been reported to represent 5 to 11 per cent of all intracranial aneurysms.

In 80 per cent of the cases in the present series osseous changes were present. Calcific deposits in the walls of the aneurysms occurred in one-third of the cases.

Cerebral angiography is of paramount importance in the diagnosis of these lesions and not infrequently offers a better understanding of the atypical and even misleading aspects of the cavernous sinus syndrome.

The ligation of the carotid artery is the treatment of choice only in carefully selected cases because of possible residual sequelae.

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INTERESTING ASPECTS OF CEREBRAL ANGIOGRAPHY WITH EMPHASIS ON SOME UNUSUAL CONGENITAL VARIATIONS*

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SINCE the introduction of cerebral angiography by Egas Moniz,[8] in 1927, a vast amount of information has been accumulated on this specialized roentgenologic procedure. The interesting anomalies and variations of the cerebral arteries, long the study of the anatomist, have been documented both morphologically and functionally in the living by angiography. The relationship of these variations and anomalies to different stages of development of the cerebral vascular system in the embryo has provided a basis for the interpretation of their significance. This paper is concerned with some of these interesting and unusual variations and anomalies of the cerebral vascular system observed by the authors and others.

Streeter[16] and later Padget[12] published excellent monographs on the development of the human cerebral vessels. The development is characterized by a continual process of absorption and fusion of the vessels as well as general growth and maturation of the vessels. In the 4 mm. embryo there is the emergence of bilateral longitudinal neural arteries associated with extensive vascular channels which gradually absorb and fuse to form the basilar and vertebral arteries. At this stage, there are also present the 3 presegmental branches of the original paired aorta supplying the bilateral longitudinal neutral arteries (Fig. 1). These are in relation to the developing trigeminal, otic and hypoglossal neural buds and have been termed the trigeminal, otic and hypoglossal arteries, respectively. Failure of obliteration of any one of these primitive vessels results in a carotid-basilar anastomotic artery in the adult.

The otic or primitive acoustic artery soon disappears. Apparently, only 2 cases suggesting a persistence of this artery in the adult have been recorded. Krayenbühl and Yasargil[6] reported a carotid angiogram demonstrating a vessel believed to represent a primitive acoustic artery. Wiedenmann and Hipp[20] also demonstrated angiographically an intracranial carotid-basilar anastomosis below the level of the primitive trigeminal artery which they believed probably represented a primitive acoustic artery.

According to Padget,[12] the hypoglossal artery is seen to regress at about the 5.5 mm. embryonic stage with the principal caudal blood supply to the neural artery being the first cervical segmental artery. Anatomic description of the persistence of this vessel in the adult has been recorded in 4 instances by Batujeff,[1] Oertel,[10] Hirako,[5] and Morris and Moffat.[9] Lindgren is credited by Wiedenmann and Hipp[20] with the first angiographically demonstrated hypoglossal artery. Wiedenmann and Hipp[20] report 2 cases of their own from a study of 7,382 carotid angiograms. Begg[2] recorded a persistent hypoglossal artery seen in a carotid angiogram of a 58 year old man with a left basal ganglia glioma. The authors have had the opportunity to study a case of an anomalous vessel arising from the cervical part of the internal carotid artery similar to that reported by others as a hypoglossal artery.

ILLUSTRATIVE CASE

CASE 1. A 55 year old Caucasian male was ad-

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Presented at the Sixty-second Annual Meeting of the American Roentgen Ray Society, Miami Beach, Florida, September 26–29, 1961.

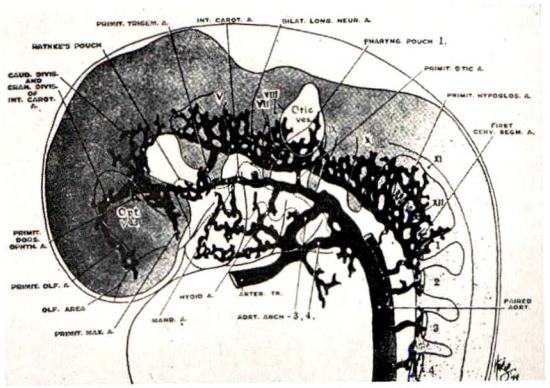


Fig. 1. Diagram of a lateral view of a 4 mm. embryo. Note the 3 presegmental arteries, the trigeminal, otic and hypoglossal, forming anastomoses between the primitive carotid and the bilateral longitudinal neural arteries. (Reproduced with permission from *Contributions to Embryology*.)

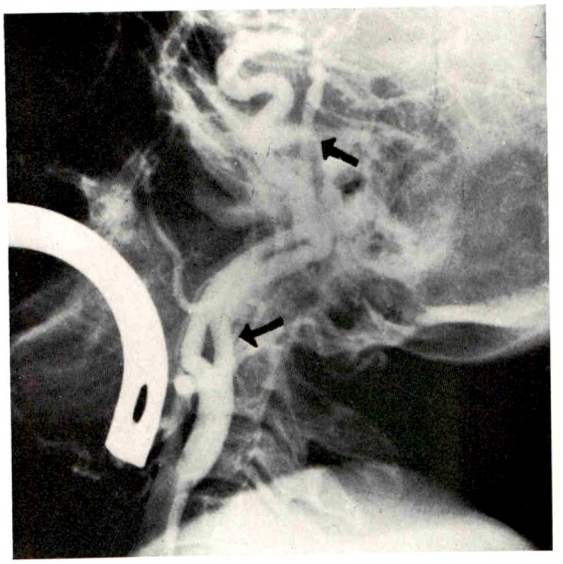


Fig. 2. Case 1. Lateral right carotid angiogram. The anomalous vessel arising from the internal carotid artery and joining the basilar artery is indicated by the arrows.

mitted complaining of right frontotemporal headaches and a noise in the right frontotemporal area. The patient had a past history of generalized seizures and a "stroke." On examination, there was a mild right hemiparesis, right homonymous hemianopsia and a decreased appreciation of pin prick over the entire right side of the body. A right carotid angiogram (Fig. 2) demonstrated a rather large common carotid artery with an internal diameter of 11 mm. which bifurcated at the level of the body of the third cervical vertebra. The internal carotid artery also had a large lumen measuring 9 mm. as compared with 5 mm. on the left side. At the level of the superior border of the body of the second cervical vertebra, it was noted that the internal carotid artery bifurcated into 2 equal sized branches. The anterior vessel appeared to proceed in a normal manner for an internal carotid artery entering the carotid canal. The posterior artery was noted to run parallel with the internal carotid artery for approximately 3 cm. and then to proceed intracranially posterior to the clivus as the basilar artery. Both posterior cerebral and superior cerebellar arteries were noted to fill (Fig. 3). A posterior communicating artery was not seen to fill. A left carotid angiogram (Fig. 4) demonstrated a rather high bifurcation of the common carotid artery at the level of the body of the third cervical vertebra. There appeared to be a partial stenosis at the origin of the internal carotid artery with a slight poststenotic dilatation. The remainder of the internal carotid artery and its major branches were normal in appearance. The posterior communicating and basilar systems were not demonstrated. Vertebral angiography was not performed. The patient was discharged to the out-patient service on anticonvulsive medication.

Anatomically, the primitive hypoglossal

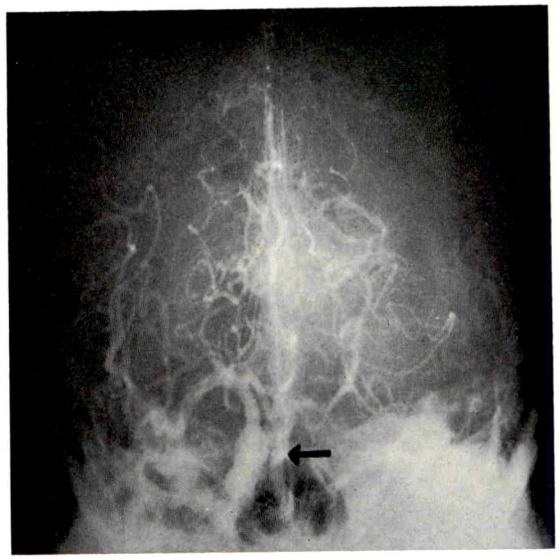


Fig. 3. Case 1. Frontal right carotid angiogram. Both the carotid and basilar (arrow) systems are seen to fill.

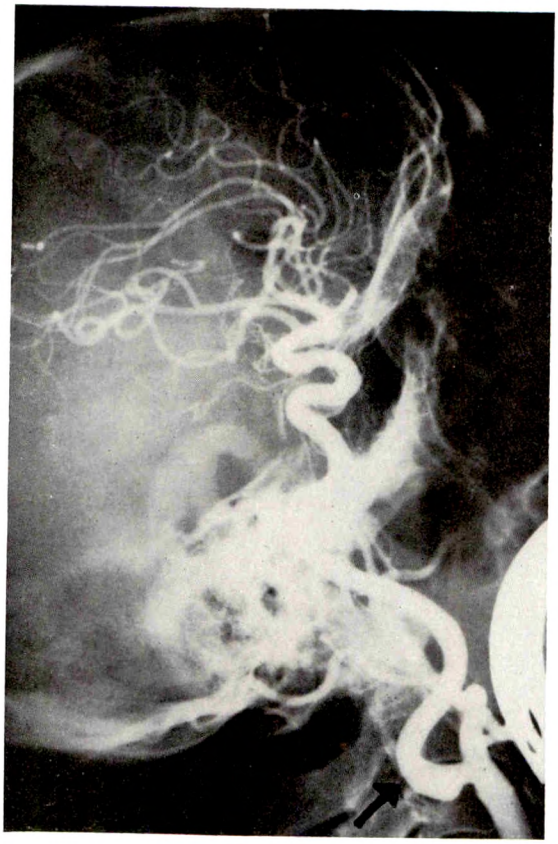


FIG. 4. Case 1. Lateral left carotid angiogram illustrating partial stenosis and poststenotic dilatation of the internal carotid artery (arrow).

artery has been described as arising from the cervical part of the internal carotid artery shortly before it enters the carotid canal. It follows the hypoglossal nerve through the hypoglossal canal into the cranium and thence into the basilar artery. It is interesting that in the anatomically described cases cited above, 3 of the cases exhibited an absent or rudimentary vertebral artery on the side of the persistent hypoglossal artery. In the 2 cases described by Wiedenmann and Hipp,[20] vertebral angiography was not carried out; however, considerable reduction in the caliber of the basilar artery was demonstrated just below the origin of the superior cerebellar arteries. Vertebral angiography was not performed in Begg's case either, but he states that "judging by the small size of the foramina transversaria, both vertebral arteries were of small diameter."

The third primitive carotid-basilar anastomotic vessel, the trigeminal artery, persists longer than the other 2, supplying the basilar system until the development of the vertebral arteries and the anterior vascular circle at about the 9–14 mm. embryonic stage. It then begins a gradual shrinkage and obliteration, but may persist up to the 43 mm. stage.[12] Failure of obliteration means a persistent carotid-basilar anastomosis in the adult.

Quain[13] in 1844 is credited with the first description of a carotid-basilar anastomosis, that being a primitive trigeminal artery. In recent years with the increasing utilization of cerebral angiography, a number of reports of persistent trigeminal artery in the adult have been appearing in the literature. Sutton[19] was the first to record a case demonstrated by carotid angiography in 1950. Wiedenmann and Hipp[20] gave an incidence of approximately 1 per cent for demonstration of this anastomosis during routine angiography. Russell and Earle[14] suggest a true frequency of this anomaly from 0.1 to 0.3 per cent. Anatomically, the persistent trigeminal artery may be extradural, circumventing the sella turcica, or it may perforate the dorsum to anastomose with the upper portion of the basilar artery.

ILLUSTRATIVE CASE

CASE II. A 56 year old white female was admitted to the hospital with the history of right-sided headaches followed by loss of consciousness. Except for known hypertension for 8 months, the past history was noncontributory.

Physical examination on admission revealed nuchal rigidity, a right lateral gaze and left hemiparesis without sensory deficit. There was no papilledema. There was slight cardiomegaly with a Grade III systolic murmur heard over the precordium. The blood pressure was 180/90. A lumbar puncture performed on admission revealed bloody spinal fluid under considerable pressure.

Over the course of one week, the patient regained consciousness, but there was no change

in the hemiparesis. Repeated lumbar puncture revealed xanthochromic fluid. On the thirteenth hospital day, right carotid angiography was performed and revealed a large anastomotic vessel joining the infraclinoid portion of the internal carotid artery and the upper third of the basilar artery (Fig. 5, *A* and *B*). This vessel was believed to represent a persistent trigeminal artery. There was no evidence of aneurysm formation or displacement of vessels. A left carotid angiogram was interpreted as normal. Vertebral angiography was not performed.

The patient was treated conservatively with particular attention to the hypertension. There was no further subarachnoid bleeding during hospitalization and slight improvement of the hemiparesis was evident upon discharge from the hospital.

The difficulties in the angiographic demonstration of a carotid-basilar anastomosis have been pointed out by several authors.[4,7,17,20] Variations in the circulation of blood through the various components of the circle of Willis is an important factor. Often the basilar system is noted to fill on carotid angiography and vice versa. Rapid serial angiography or even cinematography may be needed to demonstrate the posterior communicating artery or a carotid-basilar anastomosis. Because of the interfering osseous structures in the lateral projections, such as the petrous ridge and mastoid, supplemental projections may be necessary for proper evaluation of a carotid-basilar anastomosis. The full axial projection has been recommended for study of the primitive trigeminal artery, while the half-axial projection would appear to be best suited for studying the hypoglossal artery.[7,20]

The problem of the significance of a carotid-basilar anastomosis in certain conditions, particularly in cases of subarachnoid hemorrhage, is controversial at present, although most writers believe that the relationship is questionable.[4,7,15,20] The importance of the trigeminal anastomosis in the Gasserian rhizotomy operation has been pointed out by Harrison and Luttrell.[4] The finding of a carotid-basilar anastomosis in association with an arteriovenous malformation must be taken into consideration in attempted surgery for the malformation. Sugar[17] postulates that when the primitive trigeminal artery does not persist, the site of its embryonic origin from the internal carotid artery may be responsible for aneurysm formation or a weak spot predisposing to the formation of the

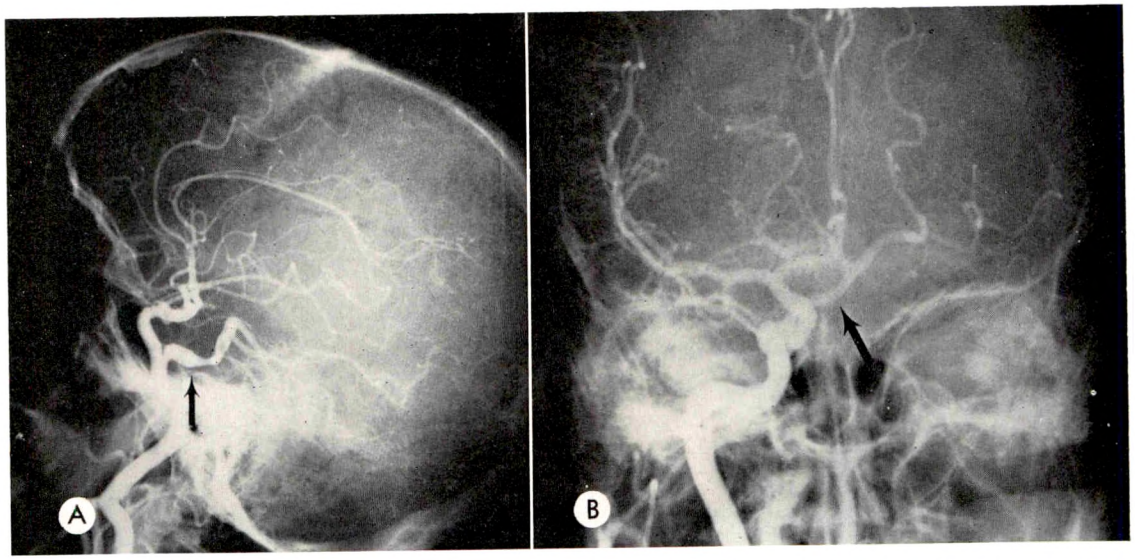


Fig. 5. Case 11. (*A*) Lateral and (*B*) anteroposterior right carotid angiograms demonstrating a large anastomotic vessel (arrows) between the internal carotid and basilar arteries representing a persistent trigeminal artery.

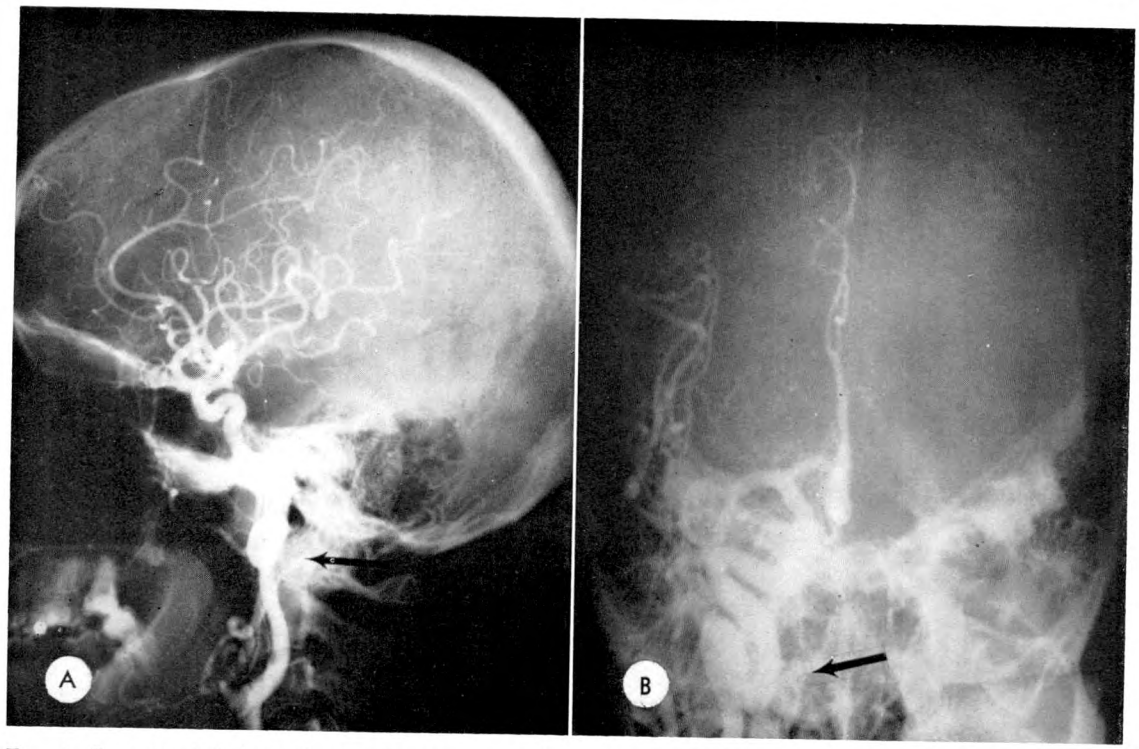


FIG. 6. Case III. (*A*) Lateral and (*B*) anteroposterior right carotid angiograms demonstrating a tortuous cervical portion of the internal carotid artery. The looping of the vessel is indicated by arrows.

traumatic carotid-cavernous fistula.

The internal carotid artery may present a variety of anomalies involving size, position, site of origin or course. These may be traced to abnormalities of the third and fourth arches and dorsal aorta in the embryo. The transition from the "branchial" to the "postbranchial" phase in the 12–14 mm. embryo constitutes an important stage in the development of the arteries arising from the aortic arch. During this stage, the proximal internal carotid artery arising from the third arch is kinked. With the gradual descent of the heart and great vessels into the thorax in later stages, the internal carotid artery becomes straightened to assume its normal adult course. Tortuosity and kinking of the cervical portion of the internal carotid artery is not an uncommon angiographic finding. In a recent study by Metz *et al.*,[8] considerable kinking of the internal carotid artery was found in 16 per cent of 1,000 "normal" angiograms and there appeared to be some relationship with cerebral vascular symptoms. In the older individual, such tortuosity and kinking may be related to arteriosclerosis; however, in the younger age group, as in the following case, a congenital basis seems plausible.

ILLUSTRATIVE CASE

CASE III. A 38 year old Caucasian female presented with symptoms of unilateral headache and neck pain. The neurologic examination was essentially normal. A right carotid angiogram demonstrated a tortuous course of the cervical portion of the internal carotid artery with a loop being formed in the midportion (Fig. 6, *A* and *B*). The external carotid artery was noted to be rather small in caliber. There was also noted some tortuosity of the major intracranial branches of the internal carotid artery.

When such deviations in course and tortuosity occur intracranially, the arteries may produce considerable extrinsic pres-

sure upon the cranial nerves. Sunderland[18] has reported rather marked thinning of the optic nerve and adjacent surfaces of the brain by a tortuous carotid artery (Fig. 7).

Similarly, alterations in the course and position of the vertebral and basilar arteries may be noted. These changes are not surprising in view of the mode of origin of these vessels from paired longitudinal neural arteries with numerous plexuses of vessels. The defects in the vertebral or basivertebral main stem are due to embryonal maldevelopment occurring primarily between the 7–18 mm. stages. The vertebral artery arises from the upper cervical segmental arteries and their anastomoses. As a result, the primitive completed vertebral artery is quite tortuous in its course. Crossing of both vertebral arteries in the midline before joining to form the basilar artery was encountered by the authors in the vertebral angiogram of a 42 year old Caucasian male (Fig. 8).

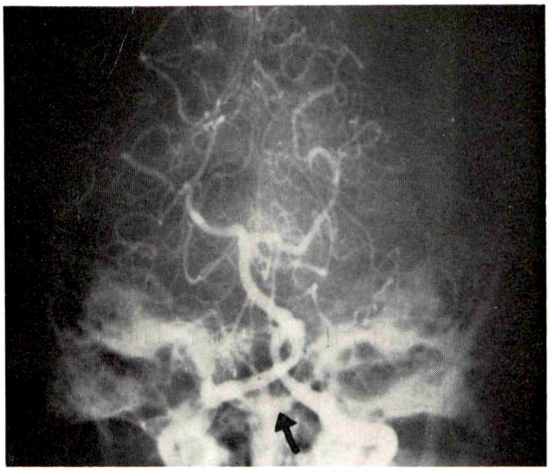


Fig. 8. Anteroposterior vertebral angiogram demonstrating unusual crossing of both vertebral arteries (arrow) before joining to form the basilar artery.

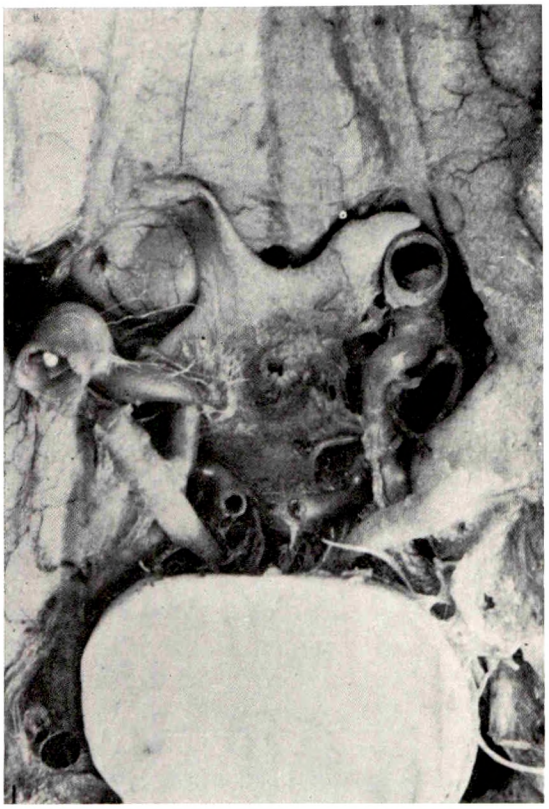


Fig. 7. View of the base of the brain from an anatomic specimen showing marked grooving and thinning of the right optic nerve by a tortuous internal carotid artery. (Reproduced with permission from *Journal of Neurology, Neurosurgery and Psychiatry*.)

Again intracranial deviations of the basilar or vertebral artery may compress one or more of the brain stem cranial nerves. According to Sunderland,[18] there is greater tendency for the basilar artery to bend to the left thereby compressing the left abducens nerve.

In discussing congenital anomalies of the cerebral vascular system, the arteriovenous malformations deserve mention. Although the mode of formation of these lesions is not well understood, the principal characteristic appears to be focal capillary agenesis. Olivecrona and Ladenheim,[11] in their monograph on this subject, speculate that the development of this lesion may be traced to the embryonal period characterized by formation of the capillary bed. They further state that the period of stratification of the vessels into superficial, dural and pial vessels with the development of the meninges and cranium determines whether the malformation will be located in the scalp, brain or dura. The specific

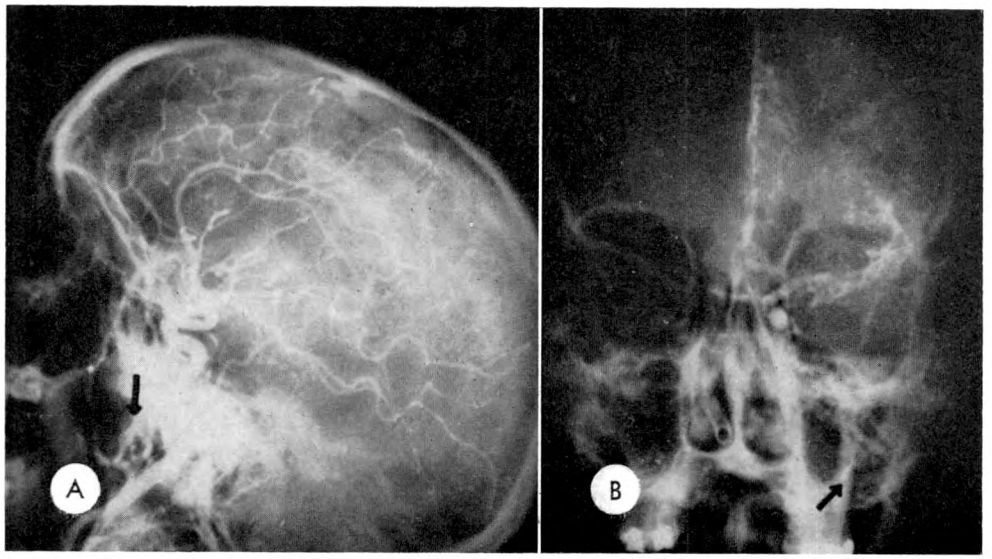


FIG. 9. Case IV. (*A*) Lateral and (*B*) anteroposterior left carotid angiograms demonstrating an arteriovenous malformation arising from the external carotid artery in the region of the pharynx (arrows).

vessels feeding the malformation may be traced to the stage of re-arrangement in the embryo where the primitive vascular channels become absorbed or fused to form the definitive adult vessels.

Although uncommon in comparison with arteriovenous malformations of the brain, arteriovenous malformations of the external carotid circulation should be remembered when studying carotid angiograms in cases clinically suspected of such lesions. The following is a case in point.

ILLUSTRATIVE CASE

CASE IV. A 23 year old Caucasian female was admitted complaining of a "squeaking" noise synchronous with the pulse and a pressure sensation in the left ear. On physical examination, a faint bruit could be heard by placing the examiner's ear directly in contact with the patient's left ear. It was not audible with a stethoscope applied over the ear. The bruit could be obliterated by pressure over the left carotid artery. The remainder of the examination was considered normal. A left carotid angiogram revealed an abnormal collection of vessels extending to the region of the nasopharynx and arising from the external carotid artery (Fig. 9, *A* and *B*). The internal carotid artery and its branches were normal. A careful re-examination of the nasopharynx revealed the presence of a bluish discoloration of the left side of the pharyngeal wall. Following ligation of the left external carotid artery, there was temporary relief of symptoms and complete disappearance of the discoloration of the nasopharynx. Subsequent ligation of the main branches of the external carotid artery reduced symptoms to the point where they were noticed by the patient only in a quiet room.

Arteriovenous malformations involving the brain present a variety of appearances angiographically, being fed by the internal carotid or vertebral circulation, often by both and sometimes additionally by the external carotid artery. Obviously, a complete angiographic evaluation of the cerebral circulation must be accomplished before any surgical attack on such lesions is undertaken.

Occasionally, plain skull roentgenographic changes will arouse one's suspicion of the possibility of an arteriovenous malformation. One such case is shown in Figure 10 where there is noted a large sinus groove sweeping down along the foramen magnum in the absence of a normal right lateral sinus groove. A right carotid angiogram in this same case (Fig. 11, *A* and *B*) demon-

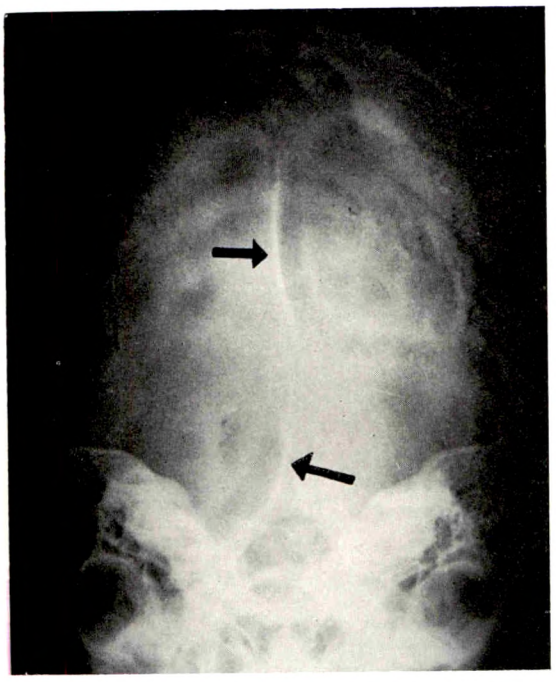


Fig. 10. Plain roentgenogram of the skull in the Towne projection showing absence of a normal right lateral sinus groove and the presence of an anomalous sinus groove (arrow) sweeping down along the foramen magnum.

strated a rather extensive arteriovenous malformation in the posterior parietal region.

Small grooves or defects on the inner table of the skull, which may be confused with pacchionian grooves, may be noted in the presence of arteriovenous malformations. These are believed to be caused by the impression of large pulsating veins carrying arterial blood as in the case shown in Figure 12, *A* and *B*.

The following case illustrates the rather rare association of a porencephaly with an arteriovenous malformation.

ILLUSTRATIVE CASE

Case v. A 49 year old Caucasian housewife was admitted with the history of a sudden onset of right hemiparesis and aphasia with a subarachnoid hemorrhage. A left carotid angiogram revealed an arteriovenous malformation in the left frontoparietal region, fed mainly by the anterior cerebral artery (Fig. 13, *A* and *B*). There was also filling of the arteriovenous malformation on the right carotid angiogram. A subsequent pneumoencephalogram (Fig. 14,

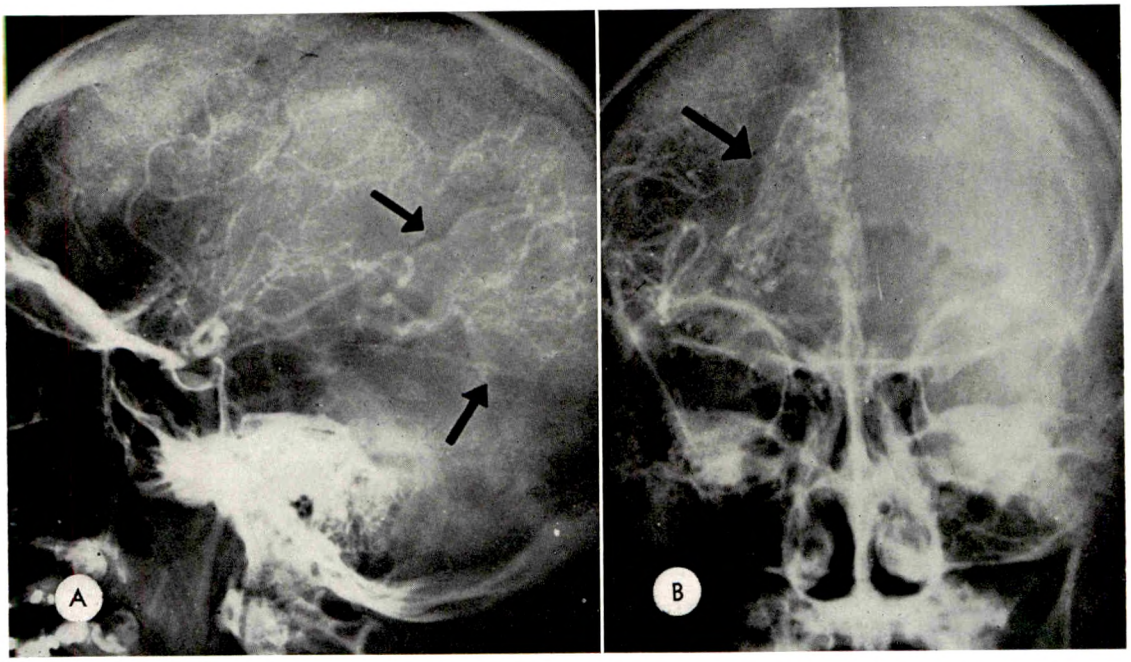


Fig. 11. (*A*) Lateral and (*B*) anteroposterior right carotid angiograms of the same case illustrated in Figure 10. An arteriovenous malformation is seen in the posterior parietal region (arrows).

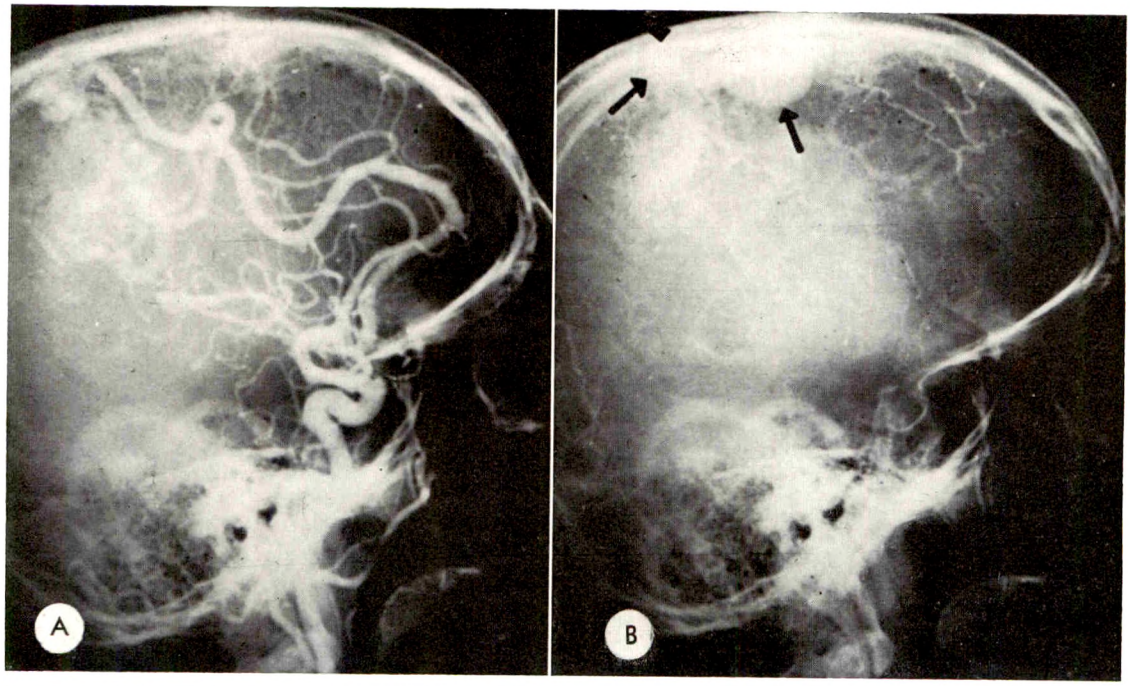


FIG. 12. (*A*) Lateral right carotid angiogram in the arterial phase demonstrating a large arteriovenous malformation in the frontoparietal region with the main arterial supply from the anterior cerebral artery. (*B*) A later phase of the same angiogram showing large abnormal veins adjacent to grooves (arrows) on the inner table of the skull.

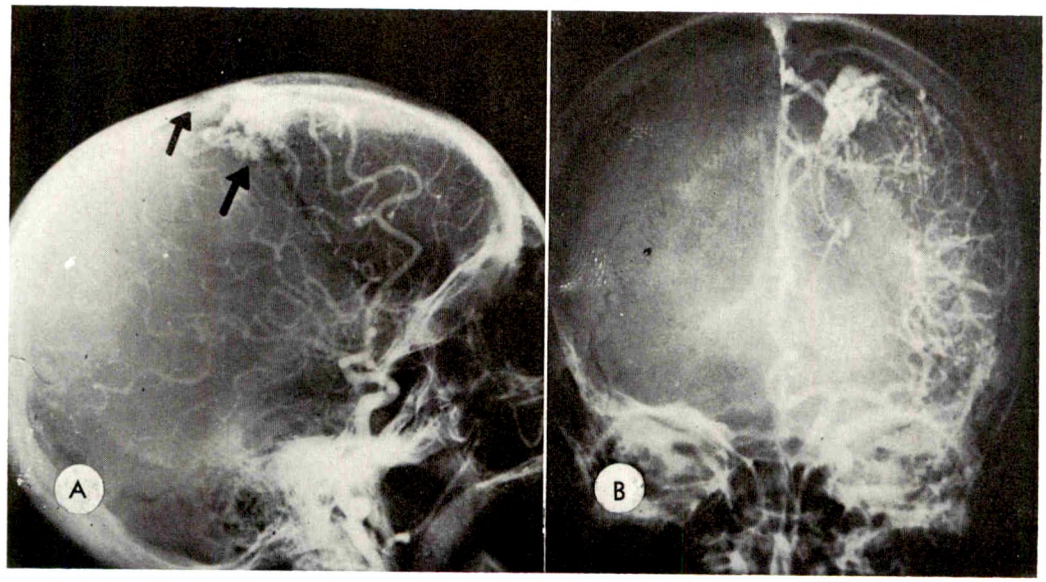


FIG. 13. Case v. (*A*) Lateral and (*B*) anteroposterior left carotid angiograms demonstrating an arteriovenous malformation in the frontoparietal region. Note the grooving on the inner table of the skull in *A* (arrows).

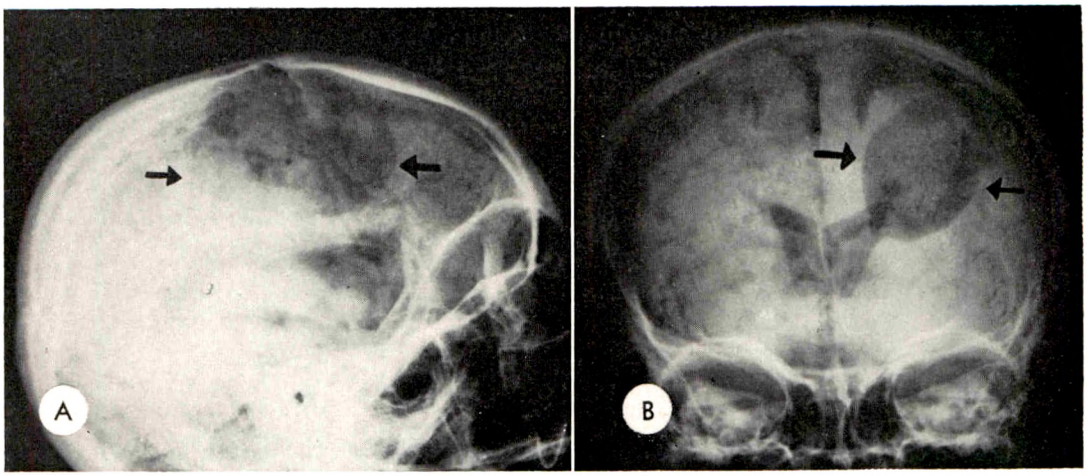


Fig. 14. Case v. (*A*) Lateral and (*B*) anteroposterior pneumoencephalograms of the same case illustrated in Figure 13 demonstrating a large porencephaly in the region of the arteriovenous malformation presumably on the basis of an intracerebral hemorrhage.

A and *B*) demonstrated a large porencephaly in the left frontoparietal region, probably the result of intracerebral hemorrhage associated with the arteriovenous malformation. The patient made a gradual improvement on conservative treatment.

One does not often have the opportunity to follow a case of Sturge-Weber disease or trigeminal encephalo-angiomatosis over a period of years. Sugar[17] and others believe that this is a congenital malformation based on the formation of telangiectasis. The basic lesion appears to be dilated pial venous channels causing stasis in the capillary bed, producing ischemia and later deposition of calcium.

ILLUSTRATIVE CASE

Case vi. The patient, a Caucasian female, was born in the Mercy Hospital, February, 1952 and appeared to be well until approximately 2 months later when she developed left sided seizures which were controlled with

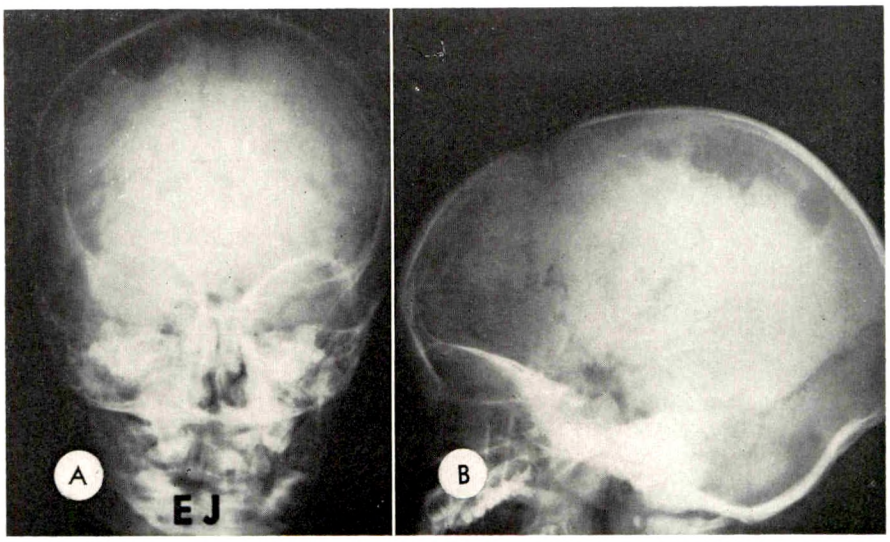
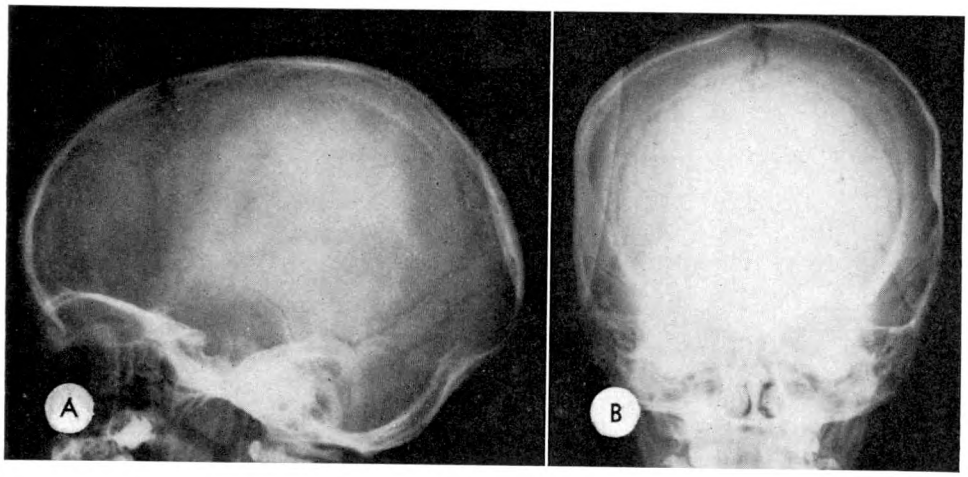


Fig. 15. Case vi. (*A* and *B*) Limited pneumoencephalograms at the age of one year showing a localized cortical atrophy in the right parietal region.



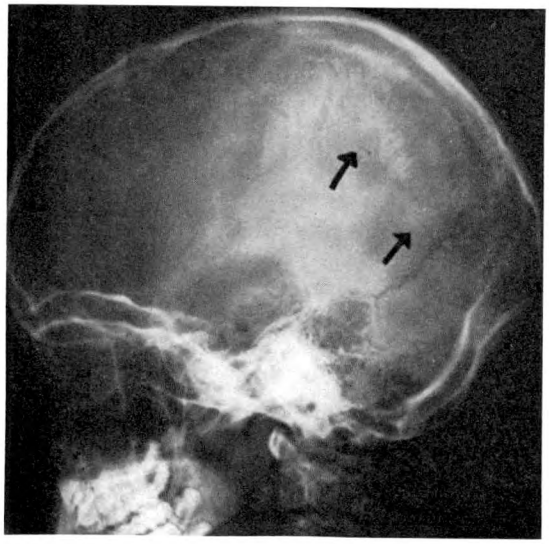


FIG. 17. Case VI. At the age of $7\frac{1}{2}$, a lateral skull roentgenogram reveals well defined typical calcification in the gyri of the parietal region.

phenobarbital. At the age of 1 year, the child did not use the left arm as well as the right. There was a port-wine mark on the right forehead extending down over the right periorbital region to the nose. A limited pneumoencephalogram made at this time (Fig. 15, *A* and *B*) demonstrated a localized atrophy in the right frontoparietal region. The patient gradually developed signs of hemiatrophy in the right calvarium which were demonstrated on a skull roentgenogram taken at the age of 2 (Fig. 16, *A* and *B*). No evidence of intracranial calcification was noted. A re-evaluation of the patient at the age of $7\frac{1}{2}$ years revealed the presence of well developed calcification of the gyri in the right parietal region and well developed hemiatrophy of the skull (Fig. 17). A pneumoencephalogram at this time, surprisingly, demonstrated the larger lateral ventricle to be on the opposite (left) side (Fig. 18, *A* and *B*). A right carotid angiogram revealed an abnormal

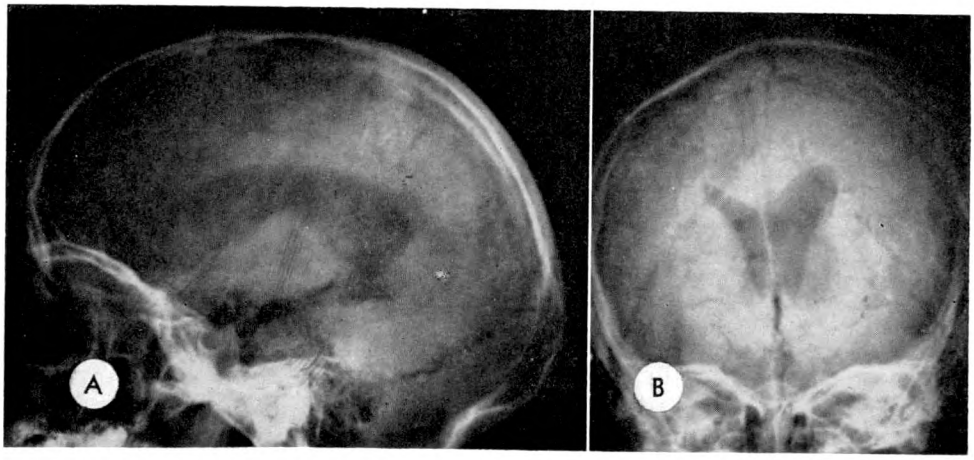


Fig. 16. Case VI. (*A*) Lateral and (*B*) anteroposterior plain skull studies performed at the age of 2. There is no definite evidence of intracranial calcification; however, there are signs of hemiatrophy on the right side.

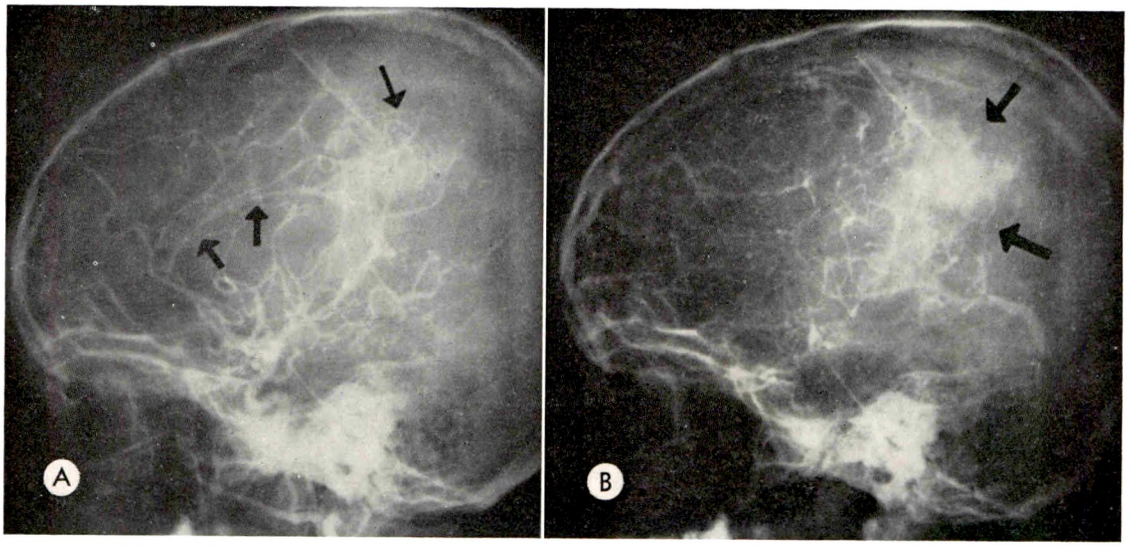


Fig. 19. Case VI. (*A*) Lateral right carotid angiogram in the arterial phase at the age of $7\frac{1}{2}$ showing a vascular malformation in the parietal region corresponding to the area of calcifications in the gyri. (*B*) A later phase of the same angiogram demonstrating a rather diffuse vascular pattern in the parietal region.

Fig. 18. Case VI. (*A*) Lateral and (*B*) anteroposterior pneumoencephalograms performed at the age of $7\frac{1}{2}$ demonstrate asymmetric lateral ventricles, the larger being on the left, the side opposite the arteriovenous malformation.

vascular pattern in the arterial phase in the parietal region corresponding to the area of calcifications in the gyri (Fig. 19*A*). In the venous phase of the angiogram, there was a rather diffuse vascular "stain" in this same area (Fig. 19*B*). There has been no appreciable change in the patient's neurologic deficit.

SUMMARY

Some of the more interesting congenital anomalies of the cerebral vascular system have been presented with an attempt to specifically correlate many of them with the embryonal development of the cerebral vessels.

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THE RING-LIKE VASCULAR PATTERN IN CEREBRAL ARTERIOGRAPHY*

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IT IS well known that the vascular pattern of a tumor demonstrated by cerebral angiography may be sufficiently characteristic to warrant a presumptive diagnosis of its histologic nature. This is especially true of glioblastomas, meningiomas and metastatic tumors.

We shall concern ourselves in this presentation with a particular type of angiographic pattern that may be observed at times in certain cases of intracranial tumor. It is characterized by a more or less circular arrangement of blood vessels about a relatively avascular area, appearing invariably in the postarterial or venous phase, frequently also in the arterial phase, and assuming a ring-like configuration. In our experience this type of vascular pattern has not been of rare occurrence, particularly in cases of glioblastoma multiforme. A review of the literature confirmed this impression. Wickbom,[12] in a study of intracranial tumors from Lindgren's clinic in 1953, commented on the significance of this type of vascular appearance as follows: "The presence of a non-vascular area with a peripheral highly vascular zone is not in itself pathognomonic of glioblastoma, since similar changes also occur with other types of glioma, as well as with metastases. But they are rarely found except in cases of malignant tumors. It is also true that a circular, highly vascular zone around a non-vascular area may be observed in cases of meningioma, although the peripheral vessels then have a much more regular appearance. With abscesses, a non-vascular area surrounded by a highly vascular zone is often seen; the peripheral vessels, however, have no irregular lumina, but appear as normal brain vessels. Occasionally, if the abscess is of long standing, a circularly coursing vein may be observed to surround the non-vascular area."

MATERIAL

It was for the purpose of ascertaining the actual frequency of occurrence of this kind of angiographic configuration as well as its diagnostic implications that an analysis of our material was undertaken. The arteriograms of 270 cases of histologically verified supratentorial intracranial tumors were reviewed. Serial roentgenograms were available in practically all of the cases. The nature of the lesions and the incidence of ring-like patterns observed in each category are listed in Table 1.

ANGIOGRAPHIC FINDINGS AND DISCUSSION

The circular arrangement of blood vessels about a relatively avascular area was ob-

TABLE I

ANGIOGRAPHY OF SUPRATENTORIAL MASSES

Diagnosis	No Ring	Ring	Total	Per Cent with Ring
Abscess	3	1*	4	25
Hemangioblastoma	0	1	1	100
Meningioma	51	0	51	0
Metastasis	64	5	69	7
Ependymoma	2	0	2	0
Oligodendroglioma	2	0	2	0
Astrocytoma	34	1**	35	3
Glioblastoma Multiforme	94	12	106	11

* Subdural Abscess.
** Malignant Astrocytoma (biopsy specimen).

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Presented at the meeting of the Eastern Conference of Radiologists, New York City, March 31, 1962.
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FIG. 1. Frontal glioblastoma multiforme showing a vascular ring of pathologic vessels.

served most often in cases of glioblastoma multiforme (Fig. 1 through 6, inclusive). By contrast a vascular ring appeared in only one of 35 cases of cerebral astrocytoma (Fig. 7). In this instance the ring did not represent neoplastic vessels but displaced veins. Histologically, this one case proved to be a malignant astrocytoma. Of all the gliomas, the glioblastoma is the one in which an abnormal vascular pattern, often distinctive in appearance, is most frequently demonstrable by means of arteriography. On the other hand, it is generally

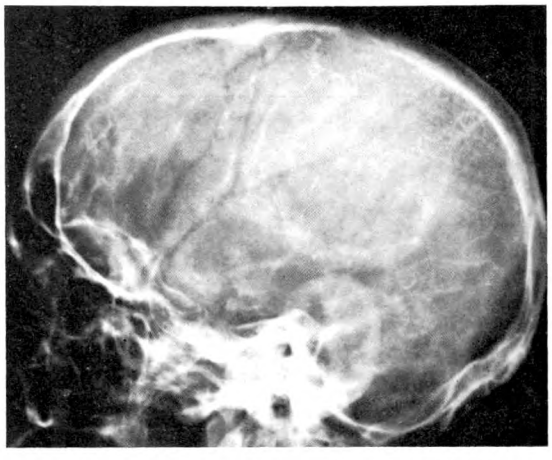


FIG. 2. Frontoparietal glioblastoma multiforme. Incomplete dense ring of abnormal vessels.



FIG. 3. Frontal glioblastoma multiforme with a circular contour (arrows) probably due to displaced circumferential veins.

agreed by most observers, including Engeset,[2] List and Hodges,[8] Torkildsen,[10] Culbreth, Walker and Curry,[1] Ethelberg and Vaernet,[3] and Lindgren,[7] that pathologic blood vessels are visualized infrequently in cases of astrocytoma. Their disclosure, as a rule, signifies the presence of a more malignant lesion.

Studies of the angioarchitecture of the

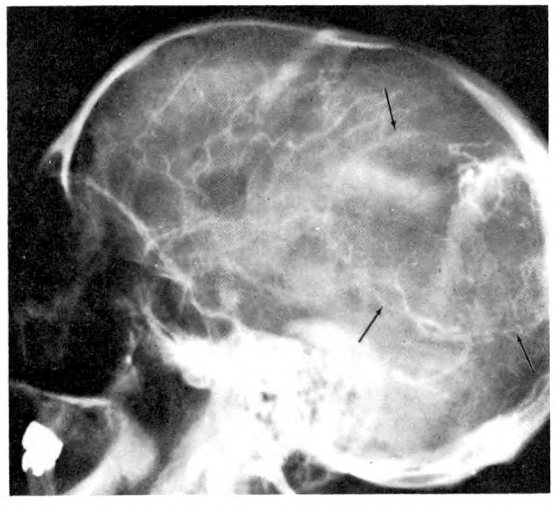


FIG. 4. Parietal glioblastoma multiforme. Displaced peripheral veins (arrows) are essentially responsible for the round appearance.

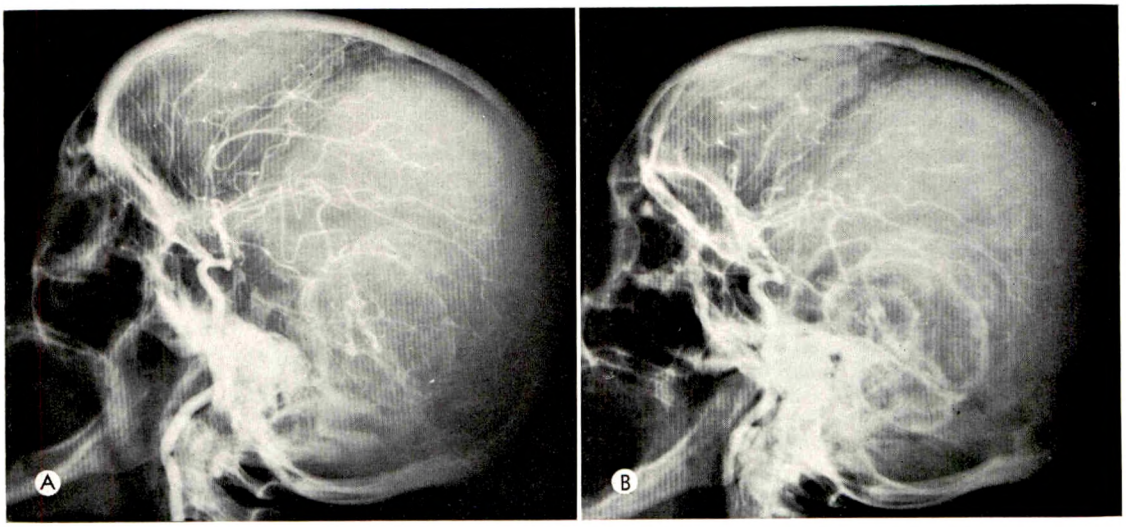


Fig. 5. Temporal glioblastoma multiforme. In (*A*) the vascular ring represents displaced arteries with pathologic vessels in its center. In a somewhat later arterial phase (*B*) abnormal blood vessels contribute to the formation of a similar pattern.

gliomas provide an explanation of the angiographic findings, especially of the ring-like pattern of neoplastic vessels observed in glioblastoma multiforme. In this type of tumor Hardman[5] was able to distinguish four zones, a peripheral one corresponding to the capillaries of the adjacent brain tissue, a second zone representing the periphery of the neoplasm in which the normal vascular pattern was disrupted and replaced by dilated capillaries and sinusoids, a deeper zone within viable tumor in which large sinusoids were the prominent feature, and, finally, a central area of necrosis with thrombosed sinusoids and extravasated blood. Continued growth of the tumor was associated with the formation of sinusoids further out in the periphery and increase in the extent of central necrosis owing to diversion of its blood

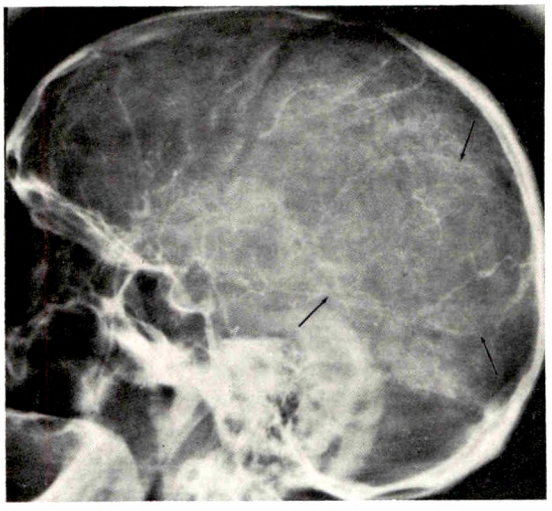


Fig. 6. Parietal glioblastoma multiforme. Circumferential veins (arrows) outline the lesion.

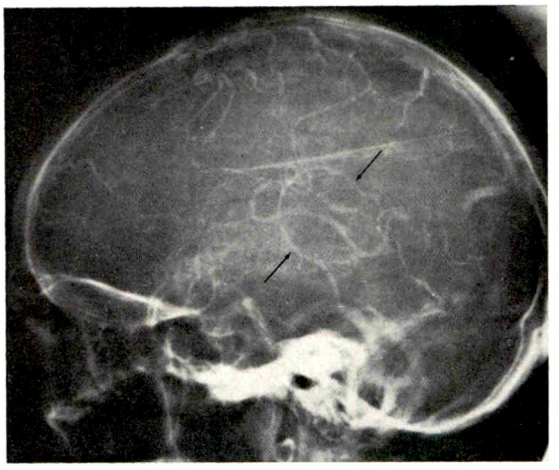


Fig. 7. Frontotemporal malignant astrocytoma. A vascular ring (arrows) of displaced veins indicates the site of the lesion.

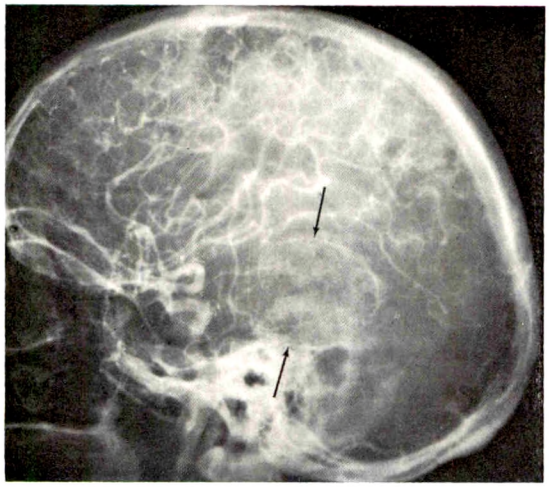


FIG. 8. Temporal lobe metastasis from carcinoma of the lung. The tumor is defined by a peripheral rim of blood vessels (arrows).

supply from within out. The vascular structure of the more benign gliomas was found to be quite different in that only capillaries forming an irregular network were present; cyst formation was commonly observed histologically. In discussing the roentgenologic significance of these observations, Hardman suggested that the demonstration of a ring of contrast medium

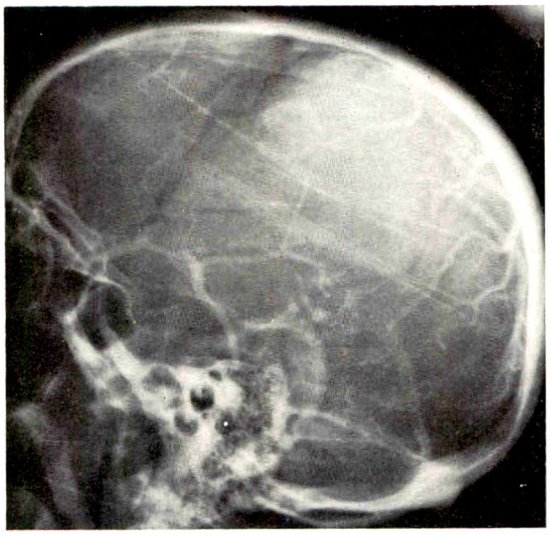


FIG. 9. Frontal lobe metastasis from carcinoma of the kidney. Pathologic vessels define the periphery of the lesion in the posterior portion of the frontal lobe.

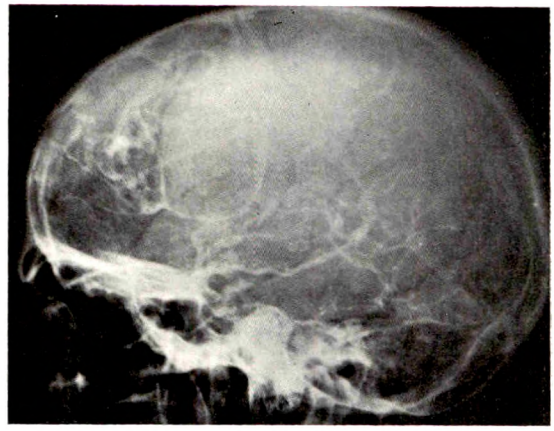


FIG. 10. Hemangioblastoma of the frontal lobe. Abnormal vessels and probably a displaced vein enter into the formation of the ring-like pattern.

about a relatively avascular center is indicative of a malignant tumor.

As mentioned earlier in this presentation, the occurrence of a circular disposition of blood vessels about a relatively avascular area in cases of glioblastoma multiforme has been noted by others. References to it, including illustrations, are to be found in the publications of Torkildsen,[10] Wickbom,[11,12] Culbreth, Walker and Curry,[1] and Lindgren.[7] Wickbom[11] observed this type of vascular pattern in 7 patients out of a total of 167 cases of glioblastoma multiforme, of which 109 were histologically verified. In our experience, it was encountered somewhat more frequently, in 12 out of 106 cases, an incidence of 11 per cent. It constantly appeared in the "intermediate" or venous phase, and in most cases during the arterial phase as well. According to Lindgren,[7] it is generally best seen in the venous phase and only sometimes visible in the arterial phase. Not infrequently in our material, displaced arteries and veins contributed wholly or in part to the appearance of the vascular ring (Fig. 3 through 6, inclusive).

Metastatic carcinoma represented the second most frequent type of tumor in which a ring-like stain could be identified. Five such tumors out of a total of 69 exhibited this pattern, an incidence of ap-

proximately 7 per cent (Fig. 8 and 9). Generally, the size of the lesion as seen on the arteriogram was smaller in the metastatic group than in the glioblastomas, the average being 4 cm. and 6 cm. respectively. A zone of increased vascularity surrounding an avascular area has been reported in cases of metastatic carcinoma by Wickbom,[11] Ethelberg and Vaernet,[3] and by Lindgren.[7] It was observed only once in Wickbom's series of 24 verified cases. Ethelberg and Vaernet found either a relatively small, round opaque shadow or a circular or semicircular bundle of delicate arteries about an avascular center in 14 out of 21 verified cases of metastatic tumor.

In none of the meningiomas in our series was a ring-like stain observed. Wickbom[11,12] and Lindgren[6,7] state that occasionally a rather wide artery may be seen encircling a tumor incompletely, in which case the lesion is probably a meningioma; gliomas and metastases may also be surrounded by blood vessels but these are usually veins. We are not convinced that this is a valid differential criterion. Lindgren has also noted that the periphery of a meningioma in contrast to its center may derive its blood supply from the internal carotid artery, in which case an injection of contrast medium into the internal carotid artery may yield a ring-like shadow reminiscent of a glioblastoma, though much more sharply circumscribed as a rule. A

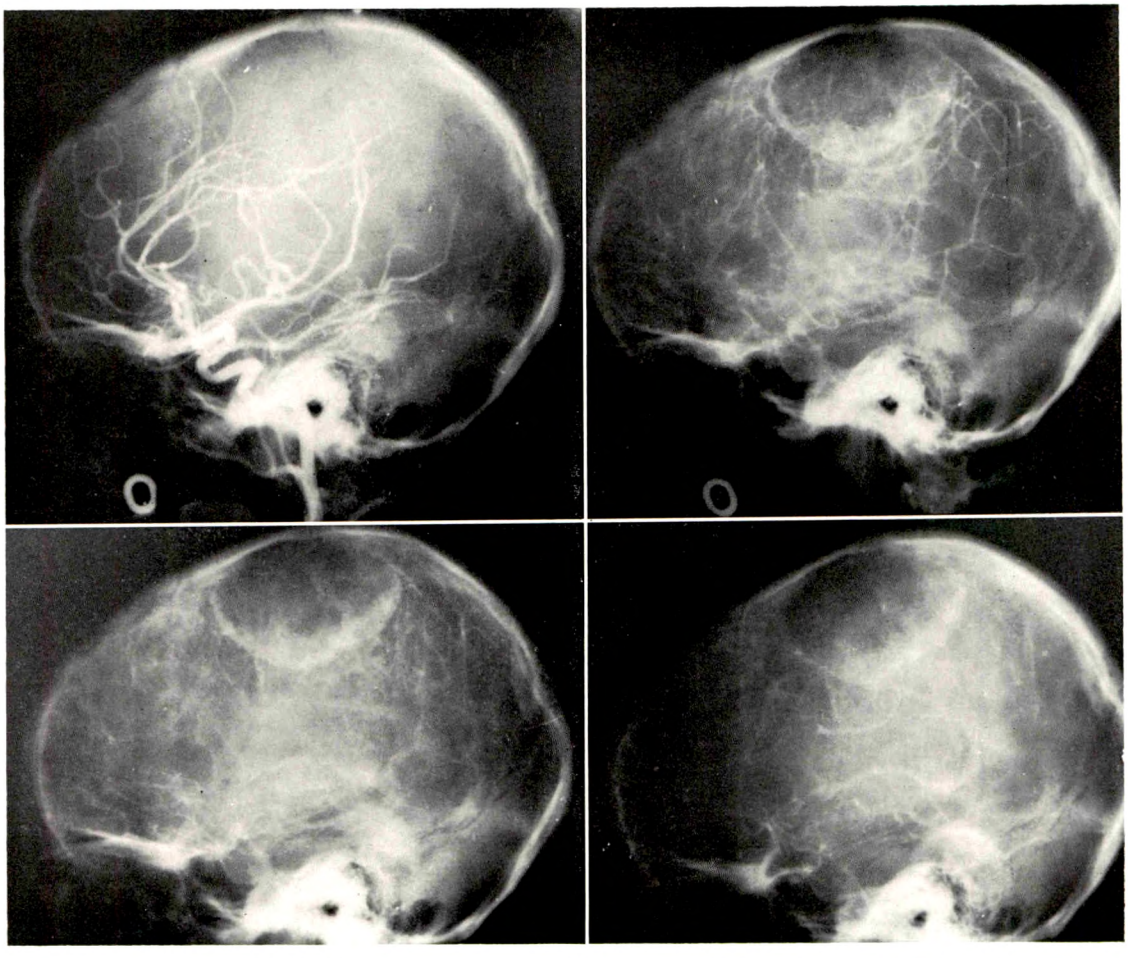


Fig. 11. Posterior frontal subdural empyema. Serial roentgenograms demonstrate a thick peripheral zone of hypervascularity with an avascular center.

striking example of one such angiogram is included in Lindgren's article.

A ring-like vascular pattern was demonstrable in the single case of a supratentorial cystic hemangioblastoma (Fig. 10). This tumor, usually found in the cerebellum, may on rare occasions contain angiomatous tissue within its cystic wall. In such cases vertebral arteriograms may show a ring of tortuous vessels surrounding the cyst. Olsson[9] and Lindgren[6,7] have described such findings.

A circular thick zone of abnormal vascularity about an avascular area was seen in a case of chronic subdural abscess (Fig. 11). While none of our 3 cases of intracerebral abscess exhibited a similar pattern, it is often present in this type of lesion, according to Wickbom[11] and Lindgren.[6,7] An illustrative arteriogram is included in the article by Greitz and Lindgren.[4]

SUMMARY

The arteriograms of a series of 270 cases of supratentorial intracranial tumors were studied for the purpose of determining the frequency and diagnostic significance of a vascular pattern characterized by a ring-like arrangement of blood vessels about a relatively avascular center.

A total of 20 cases exhibited this type of angiographic pattern. It was observed most commonly in cases of glioblastoma multiforme and metastatic carcinoma, in which the incidence was 11 per cent and 7 per cent respectively. It was also seen in one case of subdural abscess, one malignant astrocytoma and one cerebral hemangioblastoma.

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ANGIOGRAPHIC RECOGNITION OF OCCLUSIONS OF ISOLATED BRANCHES OF THE MIDDLE CEREBRAL ARTERY*

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THE intracerebral vascular occlusions responsible for small strokes have seldom been recognized roentgenographically. In a study of 80 consecutive patients with stroke, Bull, Marshall and Shaw[1] found 45 with no angiographic abnormalities. McDowell and his colleagues[7] found arterial abnormalities but no clear cut evidence of occlusion in 19 of 68 patients with stroke. They stated, "Even with the opposite side for comparison, a clear visualization and identification of occlusions in the smaller branches of the cerebral arteries is seldom possible." The frequency with which the smaller branches of the middle cerebral artery are the sites of occlusions is shown by the work of Winter and Gyori,[12] who in 21 brains with small areas of infarction found the middle cerebral artery branches involved in 18. Welch *et al.*[11] described the collateral circulation in 2 cases of middle cerebral branch occlusion but in their cases the occlusion apparently involved the main trunk distal to the origin of the posterior temporal artery rather than a single branch. Partial, as opposed to total, occlusions of the sylvian group were differentiated by Jacobsen and Skinhøj[6] but differentiation seems to have been made in the light of patency of remaining vessels rather than in a recognition of occlusion of isolated branches.

From a previous anatomic and roentgenographic study of the middle cerebral artery,[9] a method of assigning areas to the terminations of its four major branches was developed that has been very useful in recognizing occlusion of small vessels in some cases. The angiographic diagnosis of occlusion of a branch of the middle cerebral artery is the same in principle as that of other arteries and can be made by any one of three characteristic roentgenographic appearances: First, in cases of incomplete occlusion, delayed filling of a particular vessel that cannot be explained by technical or anatomic factors; secondly, abrupt termination of any vessel proximal to its normal terminal ramifications; and thirdly, absence of arteries in any area where they normally exist.

The difficulty of recognizing an absent arterial branch in the area supplied by the middle cerebral artery is due to the complexity and numerous variations in the form of division into its four major components. Despite the variation in form of the major vessels, the areas supplied by them are remarkably constant, a fact noted by Foix and Levy[3] 35 years ago, and a simple method of designating these areas as seen on the lateral projection of the carotid angiogram is as follows.

A line is drawn parallel to and 1 inch inside the inner table of the skull. A line is drawn through the axis of the sylvian vessels to meet the first line, and this sylvian line is bisected with one line drawn upward parallel to the coronal suture and another downward to a point corresponding to the internal occipital protuberance on the line parallel to the inner table of the skull. From this same point another line is drawn anteriorly to the tuberculum sellae. This divides the lateral surface into four zones, the most anterior superior being that of the ascending frontal artery (candelabra group) while just posterior to this is the smaller area of the posterior parietal artery. Posterior and inferior to this is a

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larger triangle which shares the angular area in its upper two-thirds with the termination of the posterior cerebral in its lower third. The most inferior triangle is the province of the posterior temporal and also, in the anterior portion, the smaller branches of the anterior temporal. This division is not anatomic and not exact, and should be regarded as only a series of synthetic landmarks to call attention to the normal distribution of the vessels in the various regions. Obviously, this division can only be applied to roentgenograms taken in a reasonably true lateral position.

The frontal projection is of less importance in diagnosing occlusions of isolated branches, since the ascending frontal, the posterior parietal and the angular arteries are all more or less superimposed. An occlusion of the angular artery may be manifest on a frontal projection taken with adequate angulation as a termination of the sylvian vessels inferior to their expected position. The posterior temporal artery supplies the area lateral to the sylvian fissure and absence of its branches may sometimes be apparent on careful inspection.

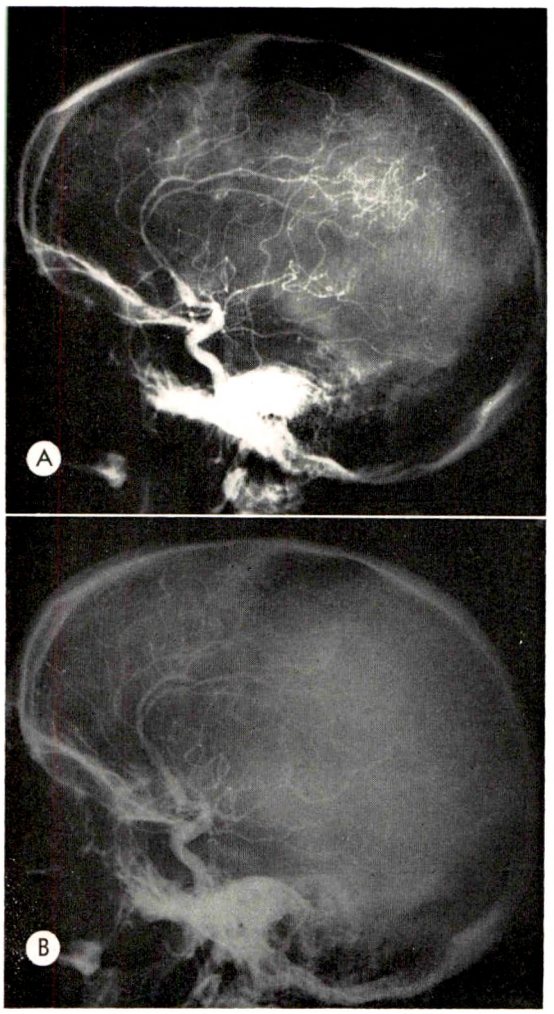
The frequency with which the four major vessels are confined to the areas assigned to them was tested on 100 supposedly normal carotid angiograms from the files, and has been used subsequently in current cases. In reviewing 100 normals, 3 cases were found in which absence of one of the branches was discovered. Since these roentgenograms were reviewed without history or clinical findings and were presupposed to be normal, the diagnosis of occlusion of an isolated branch was made purely on an anatomic basis. Review of the records of these 3 cases showed definite evidence of a stroke that could be explained by the angiographic evidence of occlusion. One possible false positive was encountered. This was an examination of a middle aged man with angiographic evidence of absence of the posterior parietal vessel, but who clinically was diagnosed as cerebral palsy and convulsive disorder. This is the only case encountered in a series that, including the current examinations since this method was adopted, numbers somewhat over 200, in which the angiographic evidence of absence of a branch was not associated with definite clinical evidence of cerebrovascular occlusion.

Over the period covered by this study, 50 cases of cerebrovascular occlusions have been diagnosed angiographically at the deGoesbriand Memorial and Mary Fletcher Hospitals. Of these, 23 were of the internal carotid, 3 of a vertebral artery, 1 of the callosomarginal branch of the pericallosal (anterior cerebral) and 23 involved the middle cerebral artery or its branches. Of these 23, 7 were of isolated branches, 2 involving two of the major branches and 5 involving one. These 7 cases are listed in Table 1 and illustrated in Figures 1 through 7, inclusive. Two of these have been previously published as illustrative material.[9] Since angiography was performed only in selected individuals, the incidence of occlusions in various sites is not necessarily that of cerebrovascular disease in general.

The first case, S. S., showed an obvious occlusion of the first examination since the vessel involved was a trunk that supplied both the angular and posterior parietal areas (Fig. 1*A*). A repeat examination 6 months later (Fig. 1*B*) showed recanalization of this vessel in a manner similar to the case reported by Gannon and Chait.[4] This recanalization may be more common

TABLE I

Case	Patient	Age	Sex	Artery Involved
1	S.S.	50	F	Left main trunk to posterior parietal and angular areas
2	H.B.	75	M	Left posterior temporal and posterior parietal
3	G.B.	50	M	Right posterior temporal
4	R.M.	66	M	Right posterior temporal
5	G.S.	42	M	Right posterior temporal
6	S.P.	56	F	Right posterior temporal
7	P.M.	59	M	Left posterior temporal



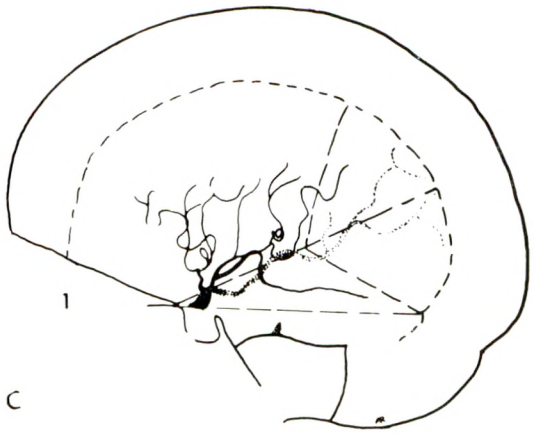


FIG. 1. Case 1. Female, aged 50. (*A*) Occlusion of a main trunk to left posterior parietal and angular areas. Numerous small vessels supplying collateral circulation from the distal pericallosal vessels are seen. (Reproduced by permission from *Acta radiologica*.) (*B*) Same patient re-examined 6 months later. There is recanalization of the occluded vessel and normal filling of all middle cerebral branches. (*C*) Composite diagram of the middle cerebral artery in both examinations; the vessels seen only on the second examination are shown in broken lines.

than is appreciated since very few cases with occlusion of intracerebral vessels have the angiographic examination repeated at a later date, and the absence of definite occlusive lesions sometimes seen in patients with residua of previous strokes may be explained on this basis in some cases.

The second case showed an abrupt occlusion of a posterior temporal branch, but a similar occlusion of the posterior parietal artery was hidden by the angular artery and might not have been recognized except for the absence of the normal vessel in the posterior parietal area. The abrupt occlusion of two separate branches would suggest the possibility of emboli although this was not definitely established.

The remaining 5 cases all showed absence of the posterior temporal branch. This is not an obvious diagnosis, since in 40 per cent of cases there are two or more components forming the blood supply of the posterior temporal area[6] and the absence of a large single posterior temporal vessel is a frequent normal finding. The absence of all significant arteries in the posterior temporal area, however, is diagnostic of an occlusion. A prominent posterior cerebral artery was filled in 4 of these 5 cases which helped to conceal the absence of the posterior temporal. The unusually high incidence of the posterior cerebral artery filling from the carotid may be only coincidental, but, since the lateral branch

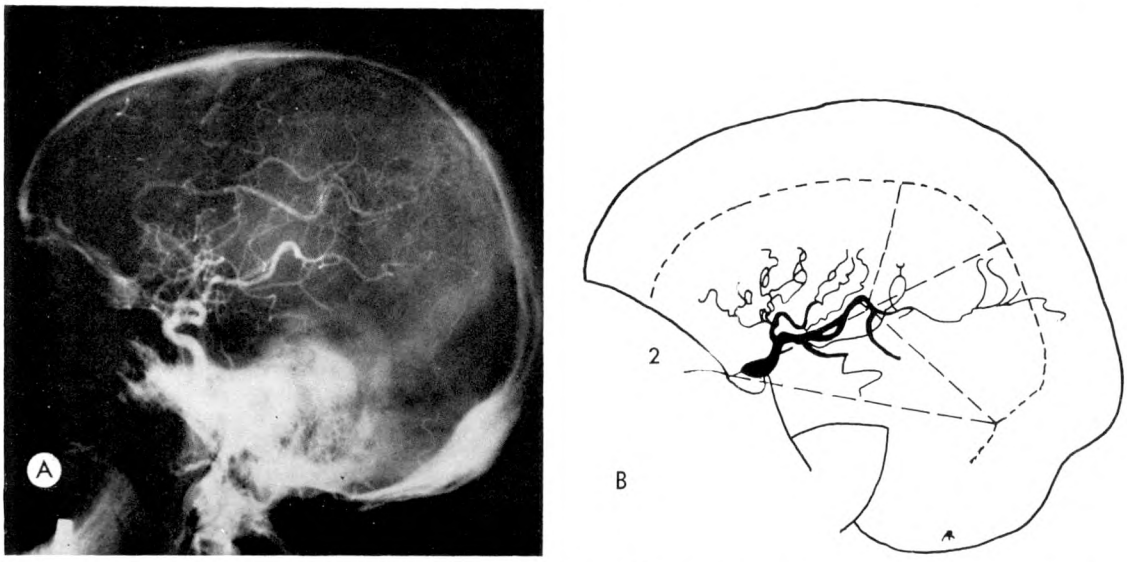


FIG. 2. Case 2. Male, aged 75. (*A*) Abrupt termination of left posterior temporal artery is seen. Similar occlusion of posterior parietal artery is concealed by the angular artery. (*B*) Diagram of *A*.

of the posterior cerebral and the posterior temporal branch of the middle cerebral supply adjoining areas, an increase in blood flow through the former to supply a collateral circulation, even though this was not roentgenographically evident, would increase the likelihood of the posterior cerebral filling from the carotid. Negri and Passerini[8] described a case of occlusion of the middle cerebral artery in which the posterior cerebral supplied the area of the sylvian vessels.

One case was seen with an incomplete occlusion, or a stenosis, of a trunk giving rise to the angular and posterior temporal arteries. These vessels filled completely only on delayed angiograms although the actual lesion could not be seen. The im-

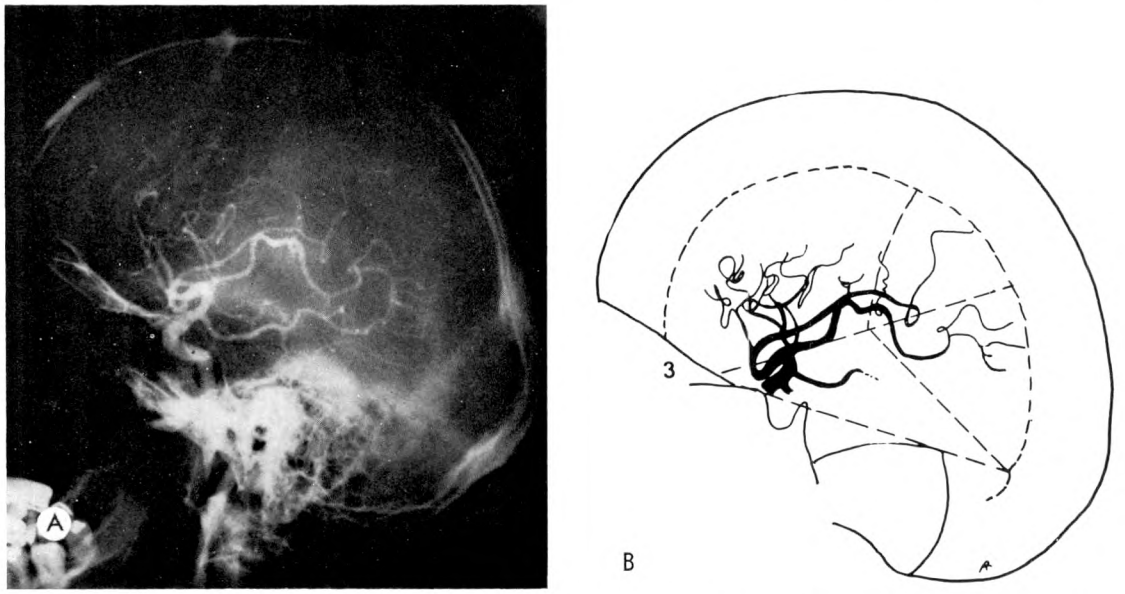


FIG. 3. Case 3. Male, aged 50. (*A*) Occlusion of right posterior temporal artery is seen. The vessel shows an irregular narrowing down to the point of obstruction. (*B*) Diagram of *A*.

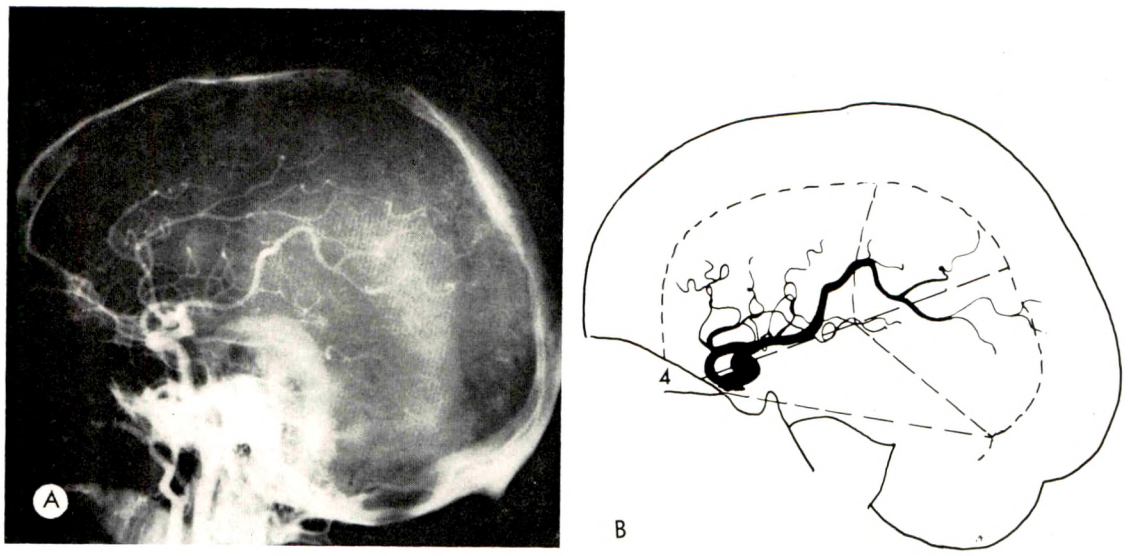


Fig. 4. Case 4. Male, aged 66. (*A*) Occlusion of right posterior temporal artery is seen. Point of occlusion is not visible. (*B*) Diagram of *A*.

portance of serial angiograms in the diagnosis of incomplete occlusion was emphasized by Greitz[5] in 1956. The delayed filling of an artery might be indistinguishable from retrograde filling by collateral circulation if only a single angiogram were available. Since the occlusion was incomplete, it was decided not to include this case in the series.

Atherosclerosis of the intracranial vessels was apparent in 5 of the 7 cases, being slight in 4 and moderately severe in 1. In none of the 7 was associated stenosis or severe atheromatous change of the internal carotid present although such a combination has been noted on postmortem studies by Samuel.[10] There is considerable practical importance in differentiating the intracerebral from the potentially surgically accessible extracerebral occlusive lesions, and these are often difficult to separate on a clinical basis, as noted by Fields and his co-workers.[2] Two of the 7 cases showed no roentgenographic evidence of vascular de-

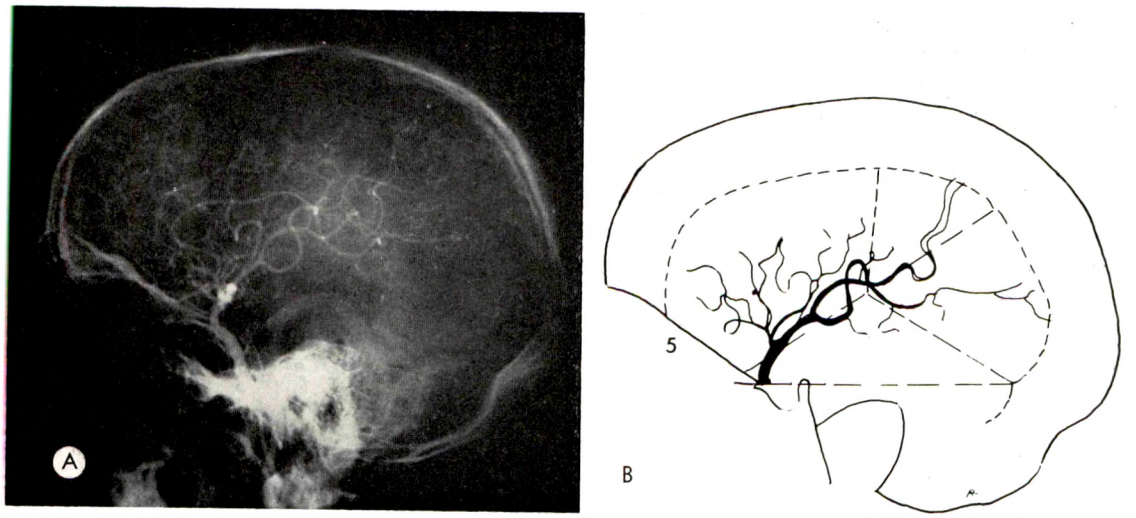


Fig. 5. Case 5. Male, aged 42. (*A*) Occlusion of right posterior temporal artery is seen. Point of occlusion is not visible. There is also straightening and elevation of carotid siphon. (*B*) Diagram of *A*.

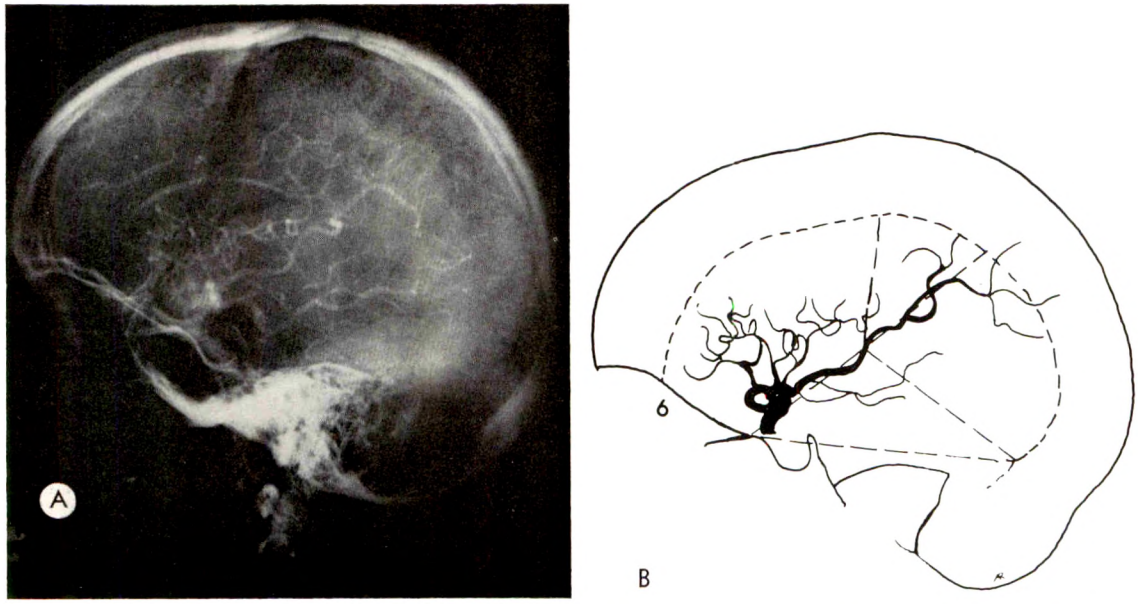


FIG. 6. Case 6. Female, aged 56. (*A*) Occlusion of right posterior temporal artery is seen. Point of occlusion is not visible. (*B*) Diagram of *A*.

generation, and one of these (Case 1) was thought to have had an embolus. No source of emboli was apparent in any of the cases but this does not exclude the possibility.

Secondary signs of occlusion were rare in this series. The pericallosal vessels have been noted to be unusually large in occlusions of the main trunk of the middle cerebral artery (Negri and Passerini[8]) but in this series the changes in the remaining sylvian vessels on the side of the occlusion were minimal or absent and of no diagnostic value. Only one case (Case 1) showed evidence of any collateral vessels and none showed a midline shift. One case (Case 5)

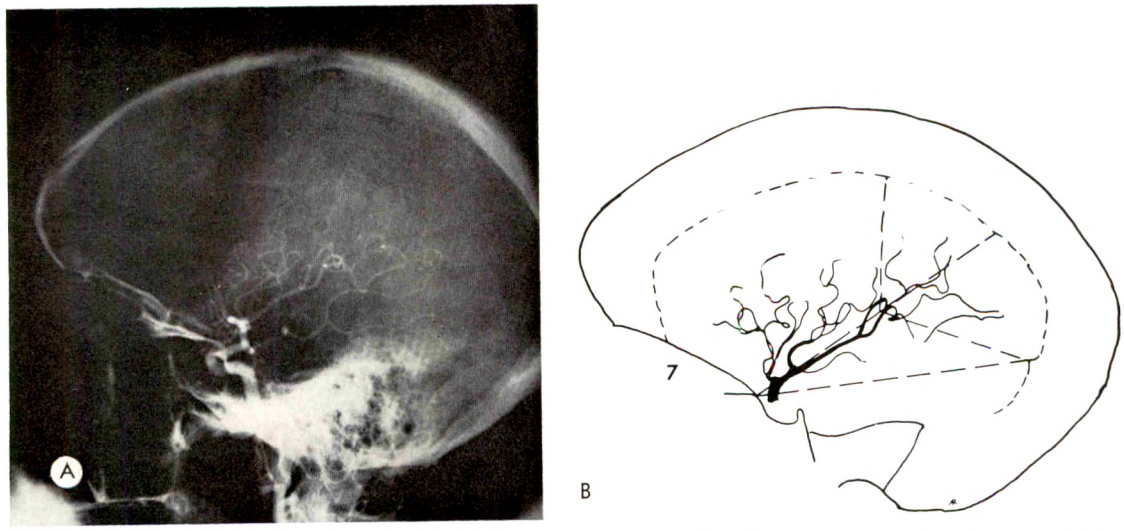


FIG. 7. Case 7. Male, aged 59. (*A*) Occlusion of left posterior temporal artery is seen. Point of occlusion is not visible. There is poor filling of pericallosal vessels. (*B*) Diagram of *A*. (Reproduced by permission from *Acta radiologica*.)

did show some elevation of the carotid siphon compatible with edema of the anterior temporal lobe.

No case of occlusion of the ascending frontal artery was encountered. Foix and Levy[3] found occlusions of the main trunk of this vessel to be rare and assumed that this was due to the very short distance that it exists as a single vessel. They did find occlusions of the branches of the ascending frontal artery not infrequently. A sufficient knowledge of the anatomy of this complex of branching might enable occlusions of its branches to be recognized, and our failure to diagnose any of these occlusions is probably due to ignorance of anatomy rather than absence of pathology.

In none of these cases was contralateral angiography performed and the opposite side was not available for comparison. Since the two middle cerebral groups in any one brain are only slightly more likely to be similar in appearance than dissimilar,[9] we would not expect a comparative view of the opposite side to be of much value.

At the present time, a number of patients with clinical strokes are still showing negative angiographic findings, and undoubtedly many of these have occlusions of small vessels that are not being recognized. The frequency with which the occlusion of isolated branches of the middle group has been diagnosed in this series indicates that this is not a rare occurrence and that many of the occlusions of smaller vessels can be diagnosed angiographically by close attention to anatomic detail.

SUMMARY

The angiographic findings in 7 cases of occlusion of isolated branches of the middle cerebral artery are presented, and a topographic method of recognizing the occlusions is discussed.

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THE SUPERFICIAL SYLVIAN VENOUS DRAINAGE SYSTEM*

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DURING the course of serial carotid angiography, the veins of the cerebral hemispheres are regularly visualized for about 4 seconds beginning 3 seconds after the injection is completed. The importance of the deep veins, specifically the internal cerebral vein and its major tributaries, in the diagnosis of cerebral tumors has been emphasized by several authors.[6,12,13] Displacement and deformity of the superficial cortical veins have also been noted and are obvious in many cases of expanding lesions.[2,5] It is rare, however, that one can be certain of the significance of minimal changes in the superficial veins in the absence of more definite findings in the arterial phases. This is disappointing since the superficial veins are located entirely separately from the arteries. Study of the arterial supply of the cerebral hemispheres and recognition of abnormalities are simplified by the fact that arterial blood is distributed via a single large vessel, the internal carotid artery. In contrast, the peripheral portions of the veins fill more or less simultaneously and drain into the dural sinuses at multiple sites. Since valves are absent, anastomotic channels may permit flow in one or the other direction. Moreover, minor variations in the number and course of the superficial veins are considerably more common than variations in the arterial supply. As a result, delineation of complete venous drainage pathways may be quite difficult.

Some of the difficulty in interpreting the venous phases of carotid angiography may be due to the opinion that gross variations of the superficial cortical veins are so common that the problem is almost hopeless. In actual fact, most of the major variations involve the superficial sylvian venous drainage pathways while the remainder of the superficial cortical vessels, on both the lateral and medial aspects of the cerebral hemispheres, have a relatively constant basic pattern (Fig. 1). This basic pattern has been clearly described by several authors.[1,3,8,11] In essence, it is based on the fact that the venous drainage from the superficial portions of the hemispheres is segmental or lobar in character and suitable draining channels must therefore be present for every part of the surface. The veins over the superior lateral aspect of the convexity draining into the superior longitudinal sinus are the best known. The number of such major channels over the convexity is distinctly limited and rarely exceeds 6. The largest of these vessels is usually in the region of the central or rolandic sulcus where the brain is widest. The superficial vein on the lateral aspect of the occipital lobe does not drain directly backward but rather upward. As a result, no large vein enters the lateral aspect of the superior longitudinal sinus for a distance of 4 to 5 cm. proximal to the torcula. The major veins on the superior medial aspect of the cerebral hemispheres correspond more or less in number to those on the lateral aspect and frequently join the lateral branches to form a common stem before entering the superior longitudinal sinus. The cingular gyrus, however, is drained by small vessels into the anterior and posterior cerebral or callosal veins. With the exception of the posterior cerebral vein, these vessels are rarely evident on angiograms. The lateral aspect of the temporal lobe is usually drained by two veins (Fig. 1) which extend posteriorly and downward to enter

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the lateral sinus. The more anterior of these two vessels is usually the smaller and enters the dura in the angle between the temporal squama and the superior surface of the petrous pyramid. In this portion of its course, this vessel appears to correspond to the so-called petrosquamosal sinus. The more posterior of these two superficial temporal cortical veins extends further backward to join the transverse sinus at some distance behind the sigmoid sinus. These two veins may be replaced by one larger superficial temporal vessel which may take the petrosquamous or a more posterior course as it runs downward and backward to enter the lateral sinus. It is of interest that these temporal veins enter the lateral sinus in a direction opposite to the flow of blood in the sinus. This feature is similar to the relationship of the superior convexity veins to the superior longitudinal sinus. On the lower lateral aspect of the occipital lobe, there is usually one superficial vein (Fig. 1) which drains downward and forward to enter the lateral sinus frequently in conjunction with a superficial temporal cortical vessel. This region of confluence immediately adjacent to the lateral sinus appears to correspond to the preoccipital notch. Small veins from the inferior lateral aspects of the temporal and occipital lobe frequently join the superficial vessels in the same area. The medial aspect of the occipital lobe shows a constant vein, the internal occipital vein, which drains forward to join the basal vein or the great vein of Galen. In addition, several small marginal veins often extend posteriorly into the superior longitudinal sinus from the posterior medial aspect of the occipital lobe. These latter vessels are ordinarily filled only during vertebral angiography.

The superficial sylvian vein is located centrally between the superior cortical vessels and the temporal cortical vessels. This vein drains the portions of the brain adjacent to the sylvian fissure. Despite the fact that the superficial sylvian vein is the earliest to be clearly delineated embryologically,[9,10] it nevertheless appears to be most susceptible to major variations. During development, the superficial veins form a radiating network on the surface of the hemisphere with the sylvian vein as the hub or center.[8] With growth of the brain, the superior and inferior vessels usually lose their direct connections with the sylvian vein. If the superficial sylvian vein fails to develop as a major channel, one or the other of the adjacent vessels will take over its drainage area. In this fashion, variations in the development of the superficial sylvian vein result in concomitant or compensatory changes in adjacent vessels.

The superficial sylvian vein is ordinarily described (Fig. 2*A*) as beginning in the posterior or horizontal limb of the sylvian fissure and running downward and forward along the fissure to the region of the pterion.



Fig. 1. Diagrammatic representation in the lateral projection of the major cortical veins. The vessels on the lateral aspect or convexity are indicated in shaded fashion while those on the medial aspect are clear. Note the lowermost of the frontal group or frontopolar vein (1) which frequently anastomoses with the angular vein. The superior superficial occipital vein (2) joins the superior longitudinal sinus at some distance above the torcula. Three channels are shown over the lateral aspect of the temporal and occipital lobes (3, 4, 5). The classic appearance of the superficial sylvian vein (6) with the uncal vein (7) joining its medial end is also shown. Note that the so-called anastomotic veins of Trolard and Labbé are not illustrated as components of the basic pattern. The "uncal vein" is a characteristic cortical vessel on the medial aspect of the temporal lobe (see text).

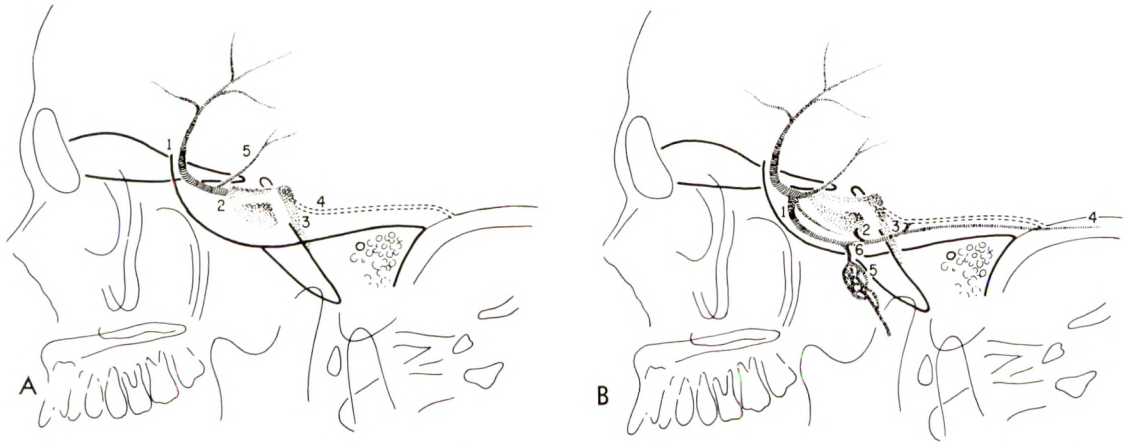


FIG. 2. (*A*) Diagrammatic representation of the angiographic appearance of the classic description of the superficial sylvian venous drainage pathway. In the region of the pterion (1), the vein turns medially and follows the lesser wing of the sphenoid to enter the anterior end of the cavernous sinus (2). The cavernous sinus is shown in stippled fashion with the lucency of the internal carotid artery within it. The basilar plexus and/or inferior petrosal sinus (3) is the main drainage pathway for the cavernous sinus. The superior petrosal sinus (4) is shown in clear fashion because it is rarely opacified in the course of carotid angiography. The uncal vein (5) is indicated as in Figure 1. (*B*) In contrast to the simple conventional representation in *A*, there frequently is a complicated system or plexus of dural channels in the anterior wall and floor of the middle fossa. These vessels have been variously designated in the anatomic literature. In this diagram, a large channel (1) lateral to the cavernous sinus is indicated as extending backwards to join or terminate in the cavernous sinus (2), the superior petrosal sinus (3), the lateral sinus (4), or the pterygoid plexus (5) via sphenoidal emissaries (6). The middle meningeal veins (not shown) also join this plexus of middle fossa dural channels.

In contrast to the arteries in the sylvian fissure, the vein is located much more superficially. In the region of the pterion, the vein enters the dura and runs along the lesser wing of the sphenoid to enter the anterior end of the cavernous sinus. The dural portion of this channel along the lesser wing is frequently referred to as the sphenoparietal sinus since, developmentally, it is said to be part of a more extensive venous drainage system which includes diploic and meningeal veins. On carotid angiography, however, there appears to be no significant dilution of the opaque material when the sinus fills via the superficial sylvian vein. This finding suggests that, at least functionally if not anatomically, the so-called sphenoparietal sinus is essentially part of the superficial sylvian venous drainage pathway. The use of the term "sinus of the lesser wing of the sphenoid" is probably more suitable than the designation sphenoparietal sinus.

While the classic description of the superficial sylvian venous drainage pathway as given above may correspond to the common finding in the adult, it has been emphasized by Padget[9,10] that, embryologically, the primary drainage of the superficial sylvian vein is not into the cavernous sinus but rather into a sinus which develops in the dura in the region of the middle fossa and extends backward to join the developing lateral sinus at some distance behind the sigmoid sinus. Since the dura in the region of the middle fossa at this stage of development is part of the tentorium, Padget has referred to this original drainage pathway of the superficial sylvian vein as the "tentorial sinus." The anastomosis or communication between the superficial sylvian vein and the cavernous sinus is late in development and, according to Padget, is frequently absent in the newborn. This author points out that the communication between the posterior portion of the cavernous sinus and

the superior petrosal sinus is of the same secondary nature and is also frequently absent in the newborn and may never develop. In addition to the tentorial sinus, there is another embryonic dural channel in the region of the middle fossa, the proötic sinus, which contributes a lateral wing to the cavernous sinus. There are also secondary connections in the floor of the middle fossa between the proötic sinus, the tentorial sinus, and the middle meningeal vein. Moreover, these channels communicate via emissary vessels through the foramina in this region extracranially with the pterygoid plexus. These emissary vessels have been referred to as the sphenoidal emissaries[9,10] and are most constant in the foramen ovale. This complicated development of the venous channels in the floor of the middle fossa and in the tentorium serves to explain the rather numerous variations in the method of drainage of the superficial sylvian vein (Fig. 2*B*).

The conventional course of the superficial sylvian vein and its drainage via the cavernous sinus is occasionally well demonstrated during the venous phases of carotid angiography (Fig. 3, *A* and *B*). The cavernous sinus may be identified by its characteristic parasellar location as well as the filling defect within it due to the internal carotid artery. The filling defect due to the syphon is frequently indistinct, particularly posteriorly and superiorly. As seen angiographically, the cavernous sinus appears to drain into the inferior petrosal sinus and the adjacent basilar plexus. The superior petrosal sinus is rarely evident as a drainage pathway of the cavernous sinus. This is in accordance with the embryologic

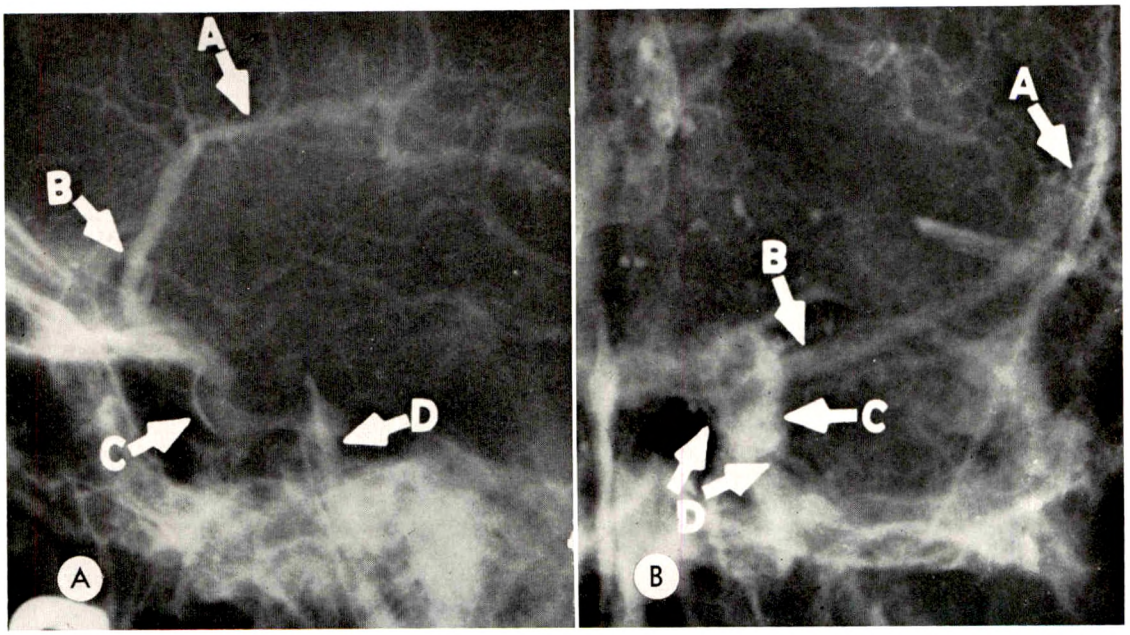


Fig. 3. The classic appearance of the superficial sylvian venous drainage pathway as seen on carotid angiography.
(*A*) Lateral projection. The vein begins in the horizontal portion of the sylvian fissure (arrow A) and runs forward and downward to the region of the pterion (arrow B). It then turns medially along the lesser wing of the sphenoid as the sinus of the lesser wing. At the medial end of the superior orbital fissure, the vein joins the cavernous sinus (arrow C) which drains posteriorly into the basilar plexus and inferior petrosal sinus (arrow D). (*B*) Anteroposterior projection. The superficial sylvian venous drainage pathway appears as one continuous arcuate channel (arrow A-arrow B) as it extends along the lesser wing of the sphenoid into the cavernous sinus (arrow C). The circular defect in the cavernous sinus is the internal carotid artery. The inferior petrosal sinus (arrows D) can be faintly seen through the cavernous sinus.

studies of Padget noted above. The size of the superficial sylvian vein, in width and in length, is quite variable. Not infrequently, this vein is small or completely absent. When this vessel is absent, the superficial sylvian drainage area may be taken over by a large channel which extends forward (Fig. 4*A*) into the frontal portion of the superior longitudinal sinus or by a large channel which extends upward or upward

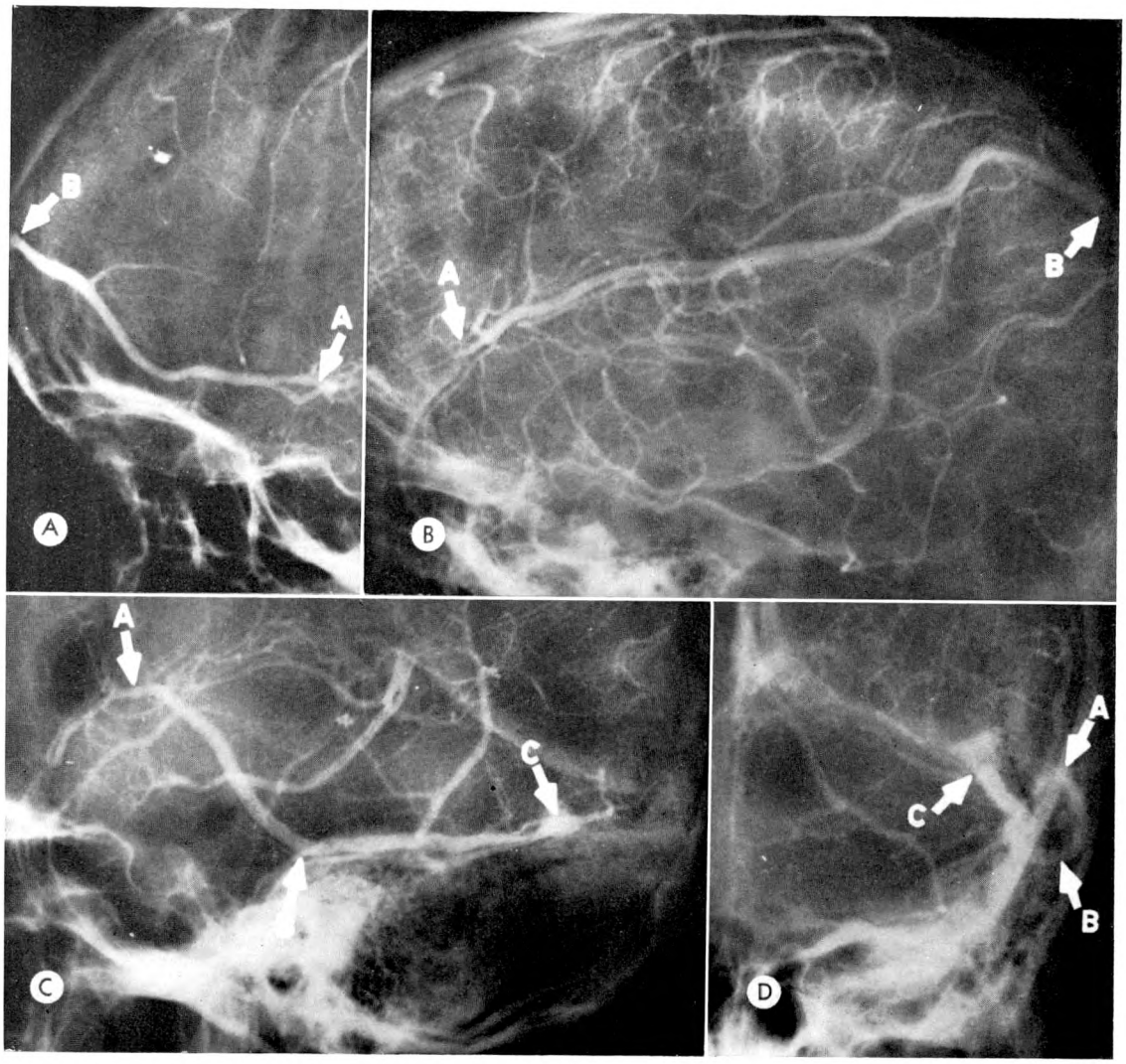


FIG. 4. Alternate drainage pathways in the absence of the superficial sylvian vein.
(*A*) A large cortical vein (arrow A–arrow B) extends from the region of the sylvian fissure forward to join the anterior portion of the superior longitudinal sinus.
(*B*) A large cortical vessel (arrow A–arrow B) extends from the region of the sylvian fissure backward and upward to join the posterior portion of the superior longitudinal sinus.
(*C*) A large cortical temporal vein extends backward and downward from the region of the sylvian fissure (arrow A) to the superior aspect of the petrous pyramid (arrow B). The vessel then extends directly backward in the angle between the petrous pyramid and the temporal squama to join the lateral sinus (arrow C) at a considerable distance behind the sigmoid sinus. (*D*) Anteroposterior projection in the same patient as in *C* shows that the portion of the vein deep to the temporal squama (arrow A–arrow B) is located immediately beneath the inner table. This is also true of the part extending posteriorly (arrow B–arrow C) parallel to the transverse sinus although this is not immediately evident because of the curvature of the skull.

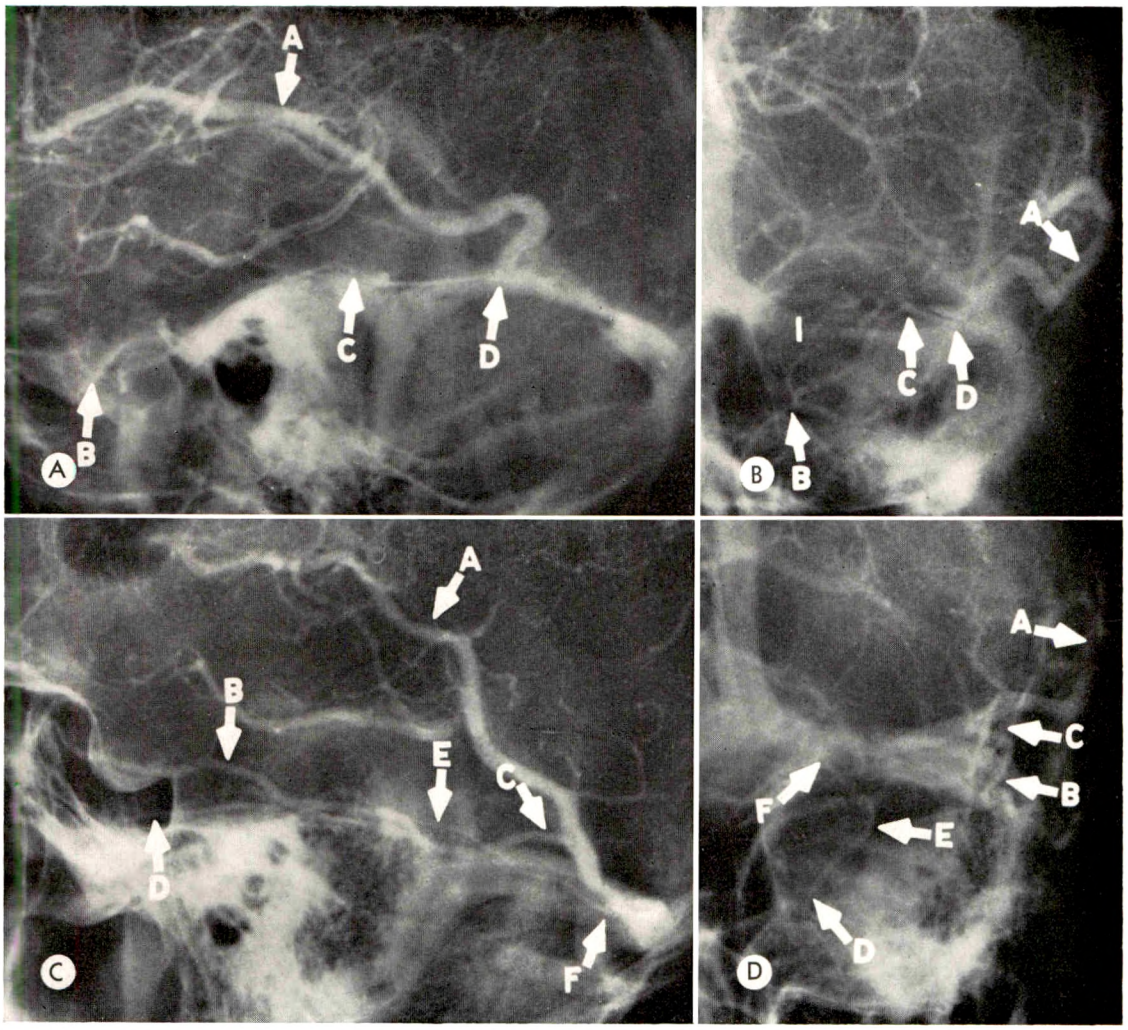


Fig. 5. Two examples of absence of the normal superficial sylvian vein and replacement by a "posterior" sylvian vein.

(*A*) Lateral projection shows absence of the usual superficial sylvian vein. Instead, there is a large vessel (arrow A) which extends posteriorly and downward in a circuitous path to the lateral sinus. In addition, there is an elongated channel on the inferior aspect of the temporal lobe (arrows B, C, D) which extends backward over the petrous pyramid into the tentorium and finally joins the lateral sinus (residual tentorial sinus of Padget or accessory sinus of Kelch). (*B*) Same patient as in *A*. The anteroposterior projection shows the anomalous superficial draining vessel (arrow A) and the temporal basal channel (arrows B, C, D). The portion of the basal channel in the tentorium (arrow C–arrow D) extends laterally to join the transverse sinus. There is in addition a small vessel (1) seen in this projection presumably related to the temporal pole which joins the basal channel in the floor of the middle fossa ("bridging" vein).

(*C*) In another patient, the lateral projection shows a similar sylvian anomalous vein (arrow A) draining the posterior portion of the fissure and extending posteriorly and downward to join the lateral sinus. There is another superficial vessel on the lowermost lateral aspect of the temporal lobe (arrow B–arrow C) which extends posteriorly in wavy fashion to join the main channel (arrow C). A straighter basal channel of special interest, however, (arrows D, E, F) is also seen. This vessel begins in the region of the temporal pole (arrow D) and continues backward into the tentorium (arrow E) to join the posterior portion of the lateral sinus (arrow F). (*D*) Same patient as in *C*. In the anteroposterior projection the two superficial vessels (arrows A, B) are seen to join posteriorly (arrow C) and then to extend further posteriorly and medially into the transverse sinus. The anomalous basal channel (arrows D, E, F) extends backward and laterally to the apex of the petrous pyramid. Its course in the tentorium (arrow E–arrow F) is directed medially into the transverse sinus near the torcula.

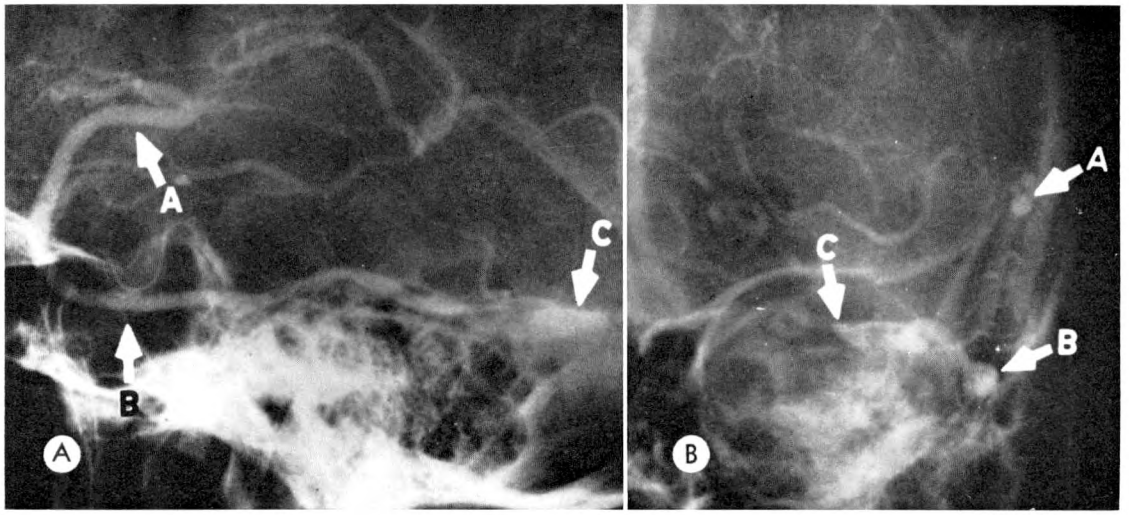


FIG. 6. Anomalous drainage of the superficial sylvian vein with failure to opacify any portion of the sinus of the lesser wing.
(*A*) Lateral projection shows a typical convexity portion of the superficial sylvian vein (arrow A). However, the vessel, instead of running medially along the lesser wing, turns directly posteriorly (arrow B) and eventually enters the lateral sinus (arrow C). (*B*) In the anteroposterior projection, the convexity portion of the superficial sylvian vein (arrow A) turns abruptly posteriorly (arrow B) immediately beneath the inner table and continues backward for a considerable distance before it joins the transverse sinus (arrow C).

and backward (Fig. 4*B*) into the same sinus. In other cases, the sylvian drainage area is taken over by a superficial temporal vein (Fig. 4, *C* and *D*) which extends downward and backward into the lateral sinus. In yet another type of drainage pattern when the superficial sylvian vein is absent (Fig. 5, *A-D*), a large vessel which starts in the horizontal portion of the Sylvian fissure drains posteriorly instead of anteriorly and takes a rather circuitous path backward and downward to join the lateral sinus. An interesting feature in two examples of this type of anomalous sylvian fissure drainage was the presence of a long venous channel on the under aspect of the temporal lobe. This channel began near the temporal pole, ran into the tentorium at the apex of the petrous pyramid, and then continued backward either laterally (Fig. 5*B*) or medially (Fig. 5*D*) to join the lateral sinus. This vessel appears to correspond rather closely with the tentorial sinus as described by Padget[9,10] and with the accessory sinus described by Kelch.[7]

The variations of the superficial sylvian vein described to this point may be considered to result from failure of the convexity portion of this vessel to develop normally. A second group of variations would include those in which the convexity portion of this vessel is not remarkable but the basal drainage pathway is, by conventional descriptions, anomalous. For example, on reaching the pterion, the vein may fail to turn medially to join the sinus along the lesser wing and instead turns directly backward (Fig. 6, *A* and *B*) along the inner aspect of the temporal squama and runs over the petrous pyramid and into the tentorium to join the lateral sinus. This configuration is quite uncommon. More commonly, the vein turns medially into the sinus of the lesser wing but fails to continue as a single channel along the entire length of the lesser wing. Before reaching the cavernous sinus, the vein turns downward in the dura of the anterior wall of the middle fossa. It may then run along the base of the middle fossa over the petrous pyramid presumably to join the superior petrosal sinus (Fig. 7, *A* and *B*). A channel

of this type[2] appears to correspond to the ophthalmopetrosal sinus of Hyrtl.[7] In most instances, however, after turning downward in the dura of the middle fossa, the opaque material appears to drain primarily via sphenoidal emissaries into the pterygoid plexus (Fig. 8, *A* and *B*). The exact drainage pathways in this type of case can ordinarily not be clearly delineated because of obscuration by adjacent bone and irregular opacification. Irregular opacification may be the result of admixture with blood from the meningeal veins. At any rate, it is not uncommon for the sinus of the lesser wing to drain, not into the cavernous sinus *per se*, but into a rather large dural channel lateral to the usual position of the cavernous sinus (Fig. 9, *A* and *B*). In addition to the accessory sinus of Kelch and the ophthalmopetrosal sinus of Hyrtl, a variety of names has been given to "anomalous" venous dural channels in the middle fossa—accessory vein of Verga, ophthalmomeningeal veins, paracavernous sinus, tentorial sinus, lateral wing of the cavernous sinus or simply "middle meningeal veins." From the roentgen point of view, the term "paracavernous sinus" seems suitable when drainage via sphenoidal emissaries into the pterygoid plexus is a prominent feature.

As the superficial sylvian vein runs downward and forward, it receives tributaries from the adjacent portions of the frontal and temporal lobes. The branches from the frontal lobe are usually more prominent than those from the temporal lobe. Anatomically, there are also described branches from the inferior aspect of the frontal lobe which join the sinus of the lesser wing, but these are rarely evident on angiography. There is, however, often a rather large cortical vein on the medial aspect of the

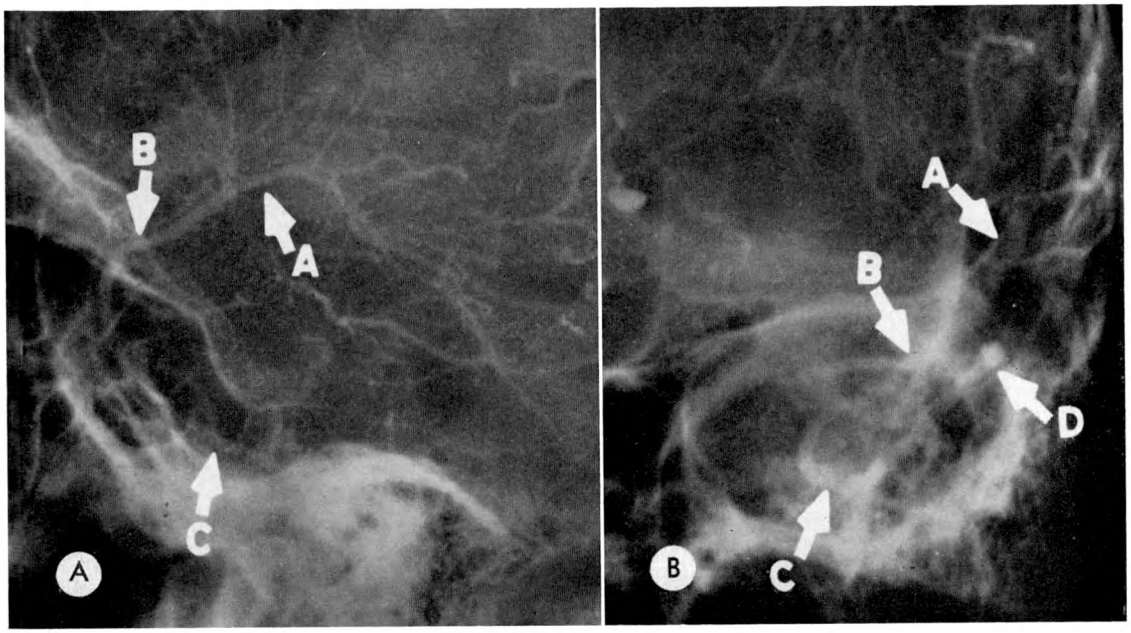


Fig. 7. Incomplete sinus of the lesser wing, "ophthalmopetrosal" sinus.
(*A*) The convexity portion of the superficial sylvian vein (arrow A) is not remarkable. From the region of the pterion (arrow B), however, a channel appears to hug the anterior wall of the middle fossa as it extends downward and backward in the floor (arrow C) of the middle fossa. As it extends further backward, it is obscured by the bone of the petrous pyramid. (*B*) Anteroposterior projection of the same patient shows that the convexity portion of the superficial sylvian vein (arrow A–arrow B) extends for only a short distance along the lesser wing and then runs downward toward the floor of the middle fossa (arrow C). It then extends backward and laterally to the apex of the petrous pyramid (arrow D) where it presumably enters the superior petrosal sinus.

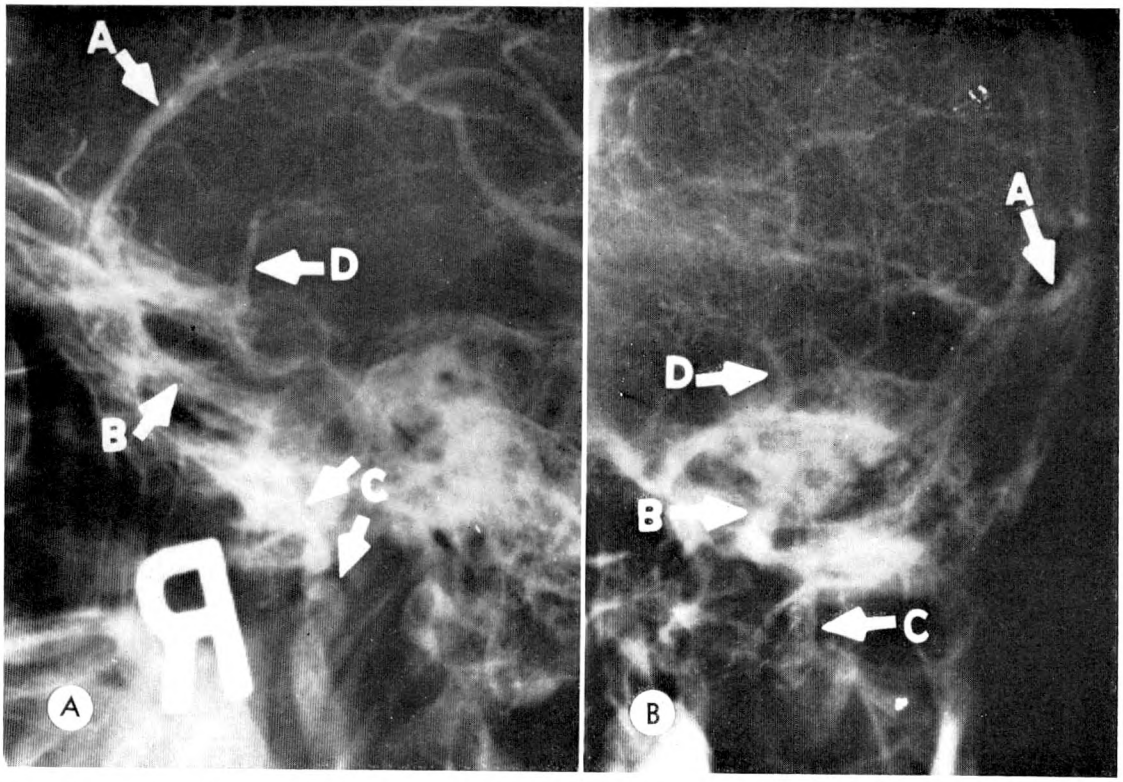


FIG. 8. Drainage of the superficial sylvian vein via middle fossa sinuses other than the cavernous sinus.
(*A*) The convexity portion of the superficial sylvian vein (arrow A) is not remarkable. The cavernous sinus, however, is not evident. Instead, there is a "paracavernous" channel (arrow B) which appears to parallel the floor of the middle fossa as it extends backward. The veins in the region of the pterygoid plexus as well as the internal maxillary or deep facial vein (arrow C) are also seen. Clear delineation of the communication between the paracavernous sinus and the pterygoid plexus is not evident because of obscuring bone. The smaller vessel (arrow D) behind the superficial sylvian vein is on the medial aspect of the temporal pole (the uncal vein). (*B*) In the anteroposterior projection, the convexity portion of the sylvian vein (arrow A) and its extension downward along the lateral portion of the lesser wing are well seen. The further course of this vessel is difficult to delineate but there is a rather thick channel (arrow B) which extends downward and then somewhat laterally and appears to be continuous with sphenoidal emissary vessels in the foramen ovale (arrow C). The uncal vein (arrow D) is shown in its usual location with a characteristic convexity laterally.

temporal lobe (Fig. 8, *A* and *B*; 9*B* and 10, *A–D*) which joins the sinus of the lesser wing in the region of the superior orbital fissure. This vessel may be quite prominent and serves to drain the anterior portion of the medial aspect of the temporal lobe as well as, in some instances, the veins of the insula (Fig. 9*B* and 10*C*). This vein has not been described in detail in the anatomic literature. The roentgen findings indicate that it is located along the anterior margin of the uncus. The term "uncal vein" is therefore a convenient designation for this vessel. In the lateral projection, it appears as a short channel which begins superiorly 1 to 1.5 cm. above the sella turcica and runs downward and forward to join the medial end of the sinus of the lesser wing or to enter directly into the cavernous or paracavernous sinus. In the anteroposterior projection, this vessel is often difficult to discern because of obscuration by bone but in suitable projections it may stand out quite prominently. It is ordinarily located about 3 cm. lateral to the mid-line. As it runs downward to the region of the superior orbital fissure,

the vein usually has a slightly curved course, convexity directed laterally. Because of its location, this vessel can serve as a landmark for the uncus or the medial aspect of the temporal pole. Since it is also located immediately adjacent to veins which join the anterior end of the basal vein, it may also serve as an anastomotic pathway between the superficial sylvian vein and the deep middle cerebral group of veins. Rarely, the basal vein may communicate more directly by a large channel (Fig. 11, *A* and *B*) with the sinus of the lesser wing. Incidentally, in the anteroposterior projection, several small veins can sometimes be seen through the orbit (Fig. 5*B* and 10*D*) joining the sinuses in the middle fossa. These may represent the "bridging" veins from the temporal pole to the sphenoparietal sinus described by Perese[11] or perhaps ophthalmomeningeal veins.

In the description of the superficial veins of the brain as given above, no mention was made of the great anastomotic vein of Trolard or the lesser anastomotic vein of Labbé. In some descriptions of the superficial cortical vessels, these veins are described as forming the basic pattern of the superficial venous drainage pathways. However, the term great anastomotic vein of Trolard is applied to any anastomotic channel between the superficial sylvian vein and the superior longitudinal sinus while the term lesser anastomotic vein of Labbé refers to any anastomosis between the superficial sylvian vein and a superficial temporal vein. Additional confusion in the

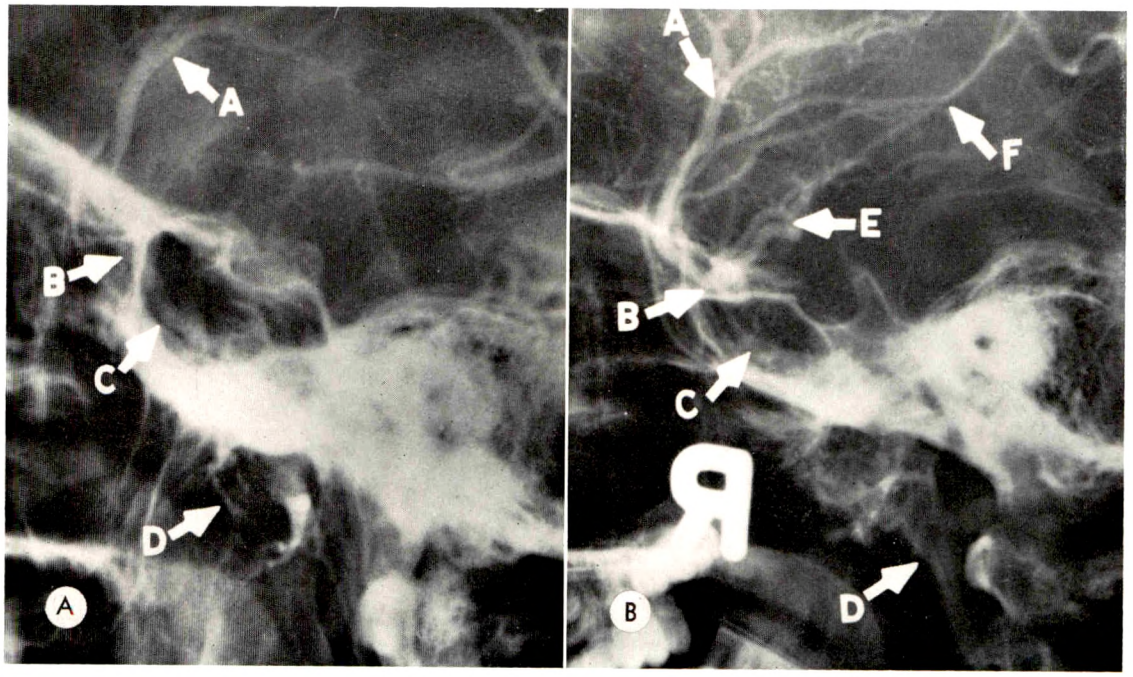


FIG. 9. Two examples of "paracavernous" and pterygoid plexus drainage of the sylvian vein.
(*A*) The convexity portion of the sylvian vein (arrow A) extends for only a short distance along the lesser wing (arrow B) and then runs downward and backward (arrow C) lateral to the cavernous sinus along the floor of the middle fossa. Sphenoidal emissary vessels, obscured by the bone of the base of the skull, drain into the pterygoid plexus (arrow D).
(*B*) Another patient shows similar findings. The convexity portion of the sylvian vein (arrow A) extends along the lesser wing of the sphenoid (arrow B) but then appears to enter a dural sinus which is not the cavernous sinus and which extends (arrow C) posteriorly along the floor of the middle fossa and drains into the pterygoid plexus and deep facial vein (arrow D). In addition, two uncal veins are seen on the medial aspect of the temporal lobe (arrow E). A prominent insula vein (arrow F) empties into the uncal vein.

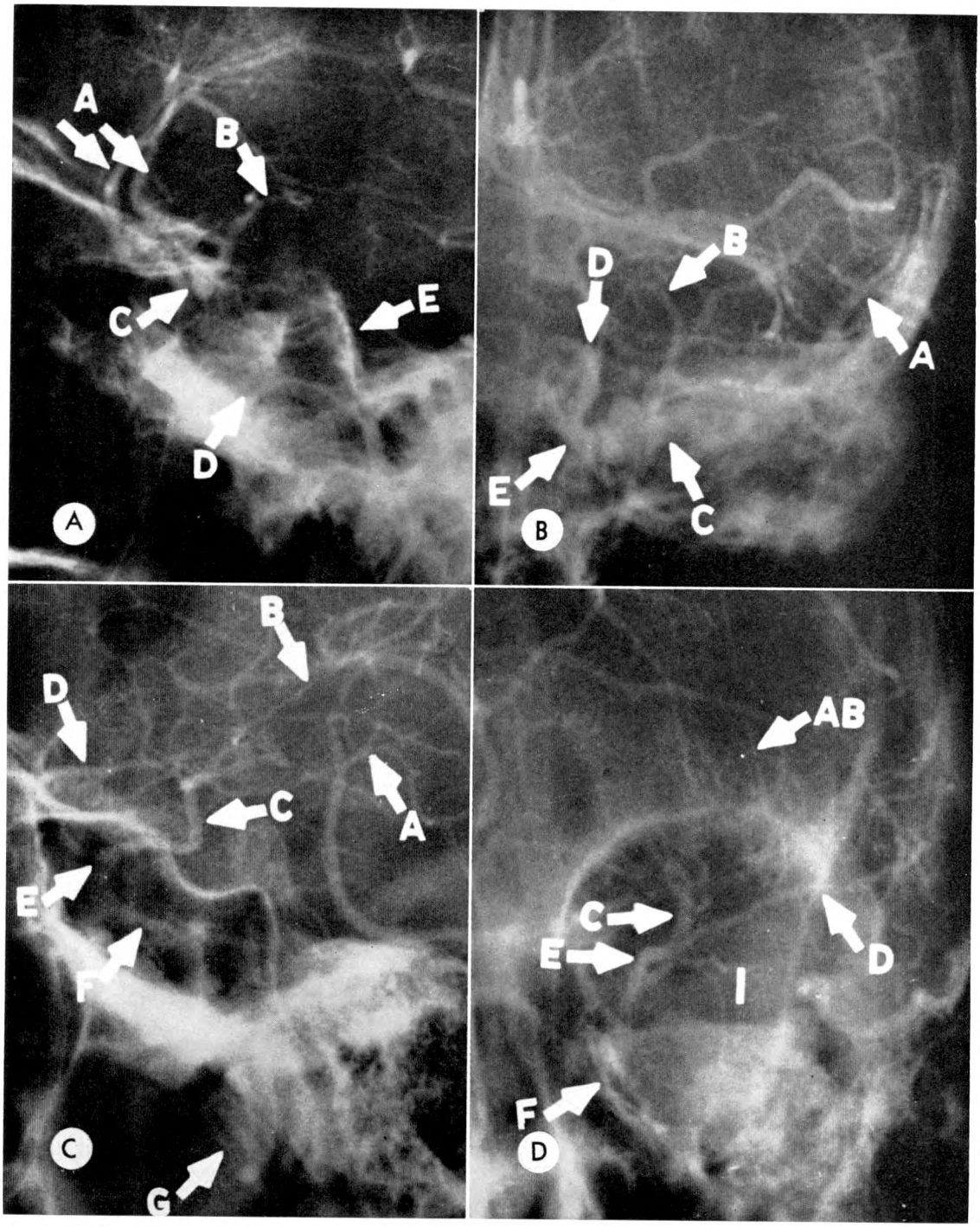


FIG. 10. Two examples of the uncal vein.

(*A*) The superficial sylvian vein is double (arrow A). The two vessels, however, appear to join in the region of the pterion. There is a prominent uncal vein (arrow B) which extends downward and forward to join the sinus of the lesser wing (arrow C) which then empties into the cavernous sinus (arrow D). The basilar or inferior petrosal sinus (arrow E) is also well seen. (*B*) Same patient as in *A*. In the anteroposterior projection, the superficial sylvian vein (arrow A) can be followed for some distance along the lesser wing. The uncal vein (arrow B) shows a typical convexity laterally as it descends to join the sinus of the lesser wing near the

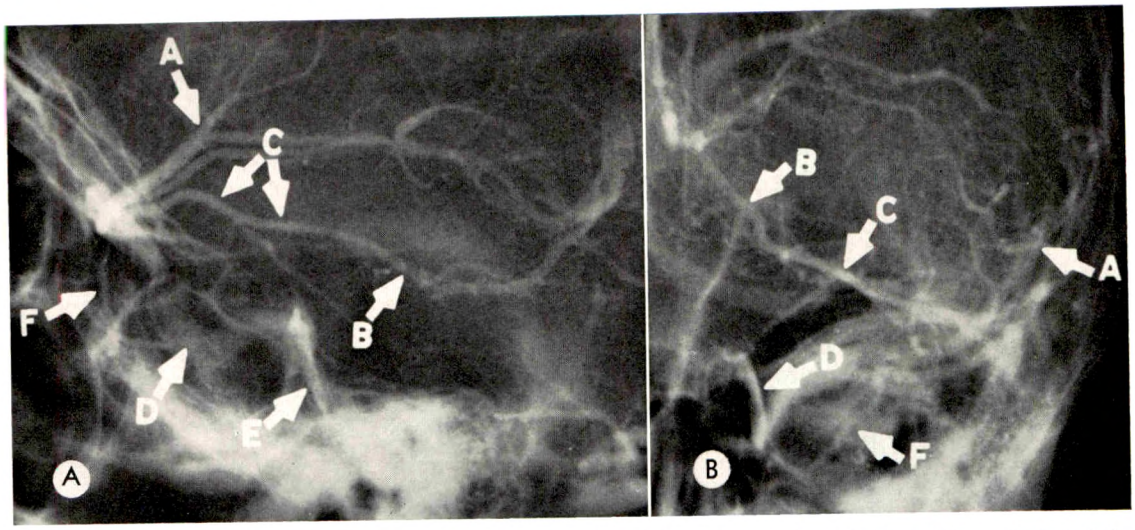


Fig. 11. An unusual example of a large anastomotic channel between the basal vein of Rosenthal and the superficial sylvian venous drainage system.
(*A*) The superficial sylvian vein (arrow A) is double. The basal vein (arrow B) is well opacified but there is an unusually large continuous channel (arrow C) between the basal vein and the superficial sylvian vein. The cavernous sinus (arrow D) is faintly opacified but the basilar plexus or inferior petrosal sinus is well opacified (arrow E). There is, in addition, a narrow channel (arrow F) which runs in the anterior wall of the middle fossa and enters the lowermost point of the cavernous sinus. (*B*) In the anteroposterior projection, the superficial sylvian vein (arrow A) and the basal vein (arrow B) are normally located. However, a long anastomotic channel (arrow C) connects these two vessels. In this projection, the cavernous sinus (arrow D) appears well opacified but the basilar plexus or the inferior petrosal sinus is not evident. The narrow channel in the anterior wall of the middle fossa (arrow F) is a continuation of the lower of the two sylvian veins.

use of the latter term has been introduced by the application of the term "vein of Labbé" to any or all of the lateral temporal cortical veins whether or not they anastomose with the superficial sylvian vein. Large anastomotic channels deserving a special designation, while not rare, are nevertheless unusual. When they occur, it appears more advisable to describe the nature of the anastomosis rather than to use the nonspecific eponymic designations.

SUMMARY

The superficial cortical veins of the cerebral hemispheres have a relatively constant appearance, location and number. They are distributed in such a fashion as to provide a segmental type of drainage of the various portions of the hemispheres independently of the arterial supply. The most variable vessel is the superficial sylvian vein. The abnormal development of this vein is associated with compensatory

superior orbital fissure (arrow C). The cavernous sinus (arrow D) and the inferior petrosal sinus (arrow E) are rather well seen.
(*C*) Lateral projection in another patient. Two insula veins (arrows A, B) join the uncal vein (arrow C) which runs vertically downward and then forward to join the small superficial sylvian vein (arrow D) at the anterior end (arrow E) of the cavernous sinus (arrow F). There is faint opacification of the veins of the pterygoid plexus (arrow G). (*D*) Same patient as in *C*. In the anteroposterior projection the insula veins are almost superimposed (arrows A, B). The uncal vein (arrow C) is characteristic in location and configuration as it extends downward to join the sinus of the lesser wing (arrow D) and to empty into the cavernous sinus (arrow F). Several small branches (1) are seen through the orbit, presumably related to the temporal pole, which also join the anterior end of the cavernous sinus.

changes in adjacent vessels. While the classic description of the drainage of the superficial sylvian vein is into the anterior end of the cavernous sinus, there are many variations which result from the complicated development of the dural sinuses along the base of the brain.

In addition to the tributaries of the superficial sylvian vein ordinarily described, there is often a prominent vessel on the medial aspect of the temporal lobe in front of the uncus designated as the "uncal vein." This should be considered part of the superficial sylvian venous drainage pathway since it usually joins the medial end of the sinus of the lesser wing or the immediately adjacent cavernous sinus.

It has been possible to identify an elongated channel along the floor of the middle fossa extending into the tentorium which appears to correspond to the tentorial sinus as described by Padget or the accessory sinus as described by Kelch.

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THE LATERAL ANASTOMOTIC MESENCEPHALIC VEIN AND OTHER VARIATIONS IN DRAINAGE OF THE BASAL CEREBRAL VEIN*

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AS POINTED out in the extraordinarily comprehensive and detailed investigation of the development of the cranial venous system by Padget,[5,6] the basal vein of the brain or vein of Rosenthal is a complex vessel formed secondarily as a longitudinal anastomotic channel which links up several veins of more primary embryologic significance. According to this author, the basal cerebral vein is formed by anastomoses between the deep middle cerebral vein, the ventral diencephalic vein, the dorsal diencephalic vein, the mesencephalic vein, and a tributary of the primitive straight sinus. The early or the original drainage of the deep veins is into the transverse sinus via a vessel within the tentorium (the "tentorial sinus"). As a result of the marked backward and lateral growth of the cerebral hemispheres in man, this route becomes long and circuitous. A shorter more direct course via an entirely new vein, the basal cerebral vein, is developed. In man, the basal vein normally drains posteriorly and medially into the great vein of Galen or into the internal cerebral vein a short distance anterior to the great vein of Galen. Exclusive posterior drainage of this type is, however, relatively unique in the human. Drainage of the basal vein in the chick, rabbit, guinea pig, cat, dog and horse is not into the great vein of Galen but into the transverse sinus.[6] In the rabbit, pig, cat, dog[1] and monkey,[2] both lateral drainage into the transverse sinus and medial drainage into the internal cerebral vein may be present on one or both sides.

In view of the complicated embryologic and ontologic development of the basal vein, it might be anticipated that variations of this vessel would be common. It is surprising therefore that such variations have rarely been reported. With the increasing use of cerebral angiography, however, it has become evident that variations of the basal cerebral vein are common. The lack of anatomic descriptions of these variations is presumably due to the circumstance that detailed anatomic studies of the veins of the brain are difficult and few in number. Padget[6] reports that in several newborn and adult brains, a prominent anastomotic channel was present between the basal vein and the great anterior cerebellar vein which replaced the usual posterior medial drainage of the basal vein into the vein of Galen. This anastomotic channel represents the persistence of a large vessel on the lateral aspect of the developing mesencephalon called the lateral mesencephalic vein. When this vessel persists as a large channel, the normal communication of the great anterior cerebellar vein with the vein of Galen is apparently lost or fails to develop. In this fashion, a single vessel composed of the anterior part of the basal vein, the lateral mesencephalic vein, and the anterior part of the great anterior cerebral vein is produced. Padget refers to this combined channel as the lateral *anastomotic* mesencephalic vein. This vein is of special interest because it represents a communication between the supratentorial and infratentorial portions of the brain. In a review of the literature by Padget,[6] only one previous illustration of a specimen showing this variation and one anatomic description was found. As pointed out below, however, this vessel—the lateral anastomotic mesencephalic vein—is not uncommonly seen on cerebral angiography and represents the most common of the variations in drainage

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of the basal cerebral vein. While this anomalous channel is obviously not entirely mesencephalic, it is useful to have a single designation for this vessel which indicates its nature and origin.

It is clear from the description of Padget of the development of the cranial venous system that variations of the basal vein other than the lateral anastomotic mesencephalic vessel are possible and likely. Veins developing on the anterior aspect of the mesencephalon are in close relationship to the basal vein and to the pontine plexus and large anastomoses between these two areas by channels in front of the pons or cerebellum might persist. This possibility appears to be confirmed on cerebral angiography although this type of anomalous drainage has not been described anatomically. Small anastomotic channels between the pontine plexus and the basal vein have, however, been described.[7] During development, there is another mesencephalic vein which drains posteriorly into the transverse sinus or the primitive tentorial plexus. The plexus is in direct communication with the embryonic marginal plexus which eventually forms the mid-line sinuses. It might be anticipated therefore that there would be examples of anomalous drainage of the basal vein into the transverse or the straight sinus via the tentorium. Drainage into the transverse sinus would correspond to the arrangement in other mammals. This type of anomalous drainage has been reported in an anatomic dissection by Johanson.[4] In this case, the basal vein drained posteriorly into the straight sinus. On cerebral angiography, drainage of the basal vein into the straight sinus a short distance behind the great vein of Galen is not rare. Cases in which a large anastomotic channel in the tentorium drains the basal vein into the transverse sinus or into the straight sinus near the torcula are more unusual.

ANOMALOUS DRAINAGE OF THE BASAL CEREBRAL VEIN

Anomalous drainage of the basal cerebral vein may be divided into two main groups. In the first group, an anastomosis between the basal vein and the petrosal sinuses is present via pial channels. In one type, drainage occurs via the lateral anastomotic mesencephalic vein and, in the other type, via the pontine or prepontine plexus. In the second group of anomalous drainage of the basal vein, the drainage is via a channel in the tentorium which terminates in the transverse sinus or in the straight sinus. Of these varieties, the most common and the most striking roentgenologically is the lateral anastomotic mesencephalic vein of Padget. The course and the appearance of this vessel will therefore be described in some detail.

THE LATERAL ANASTOMOTIC MESENCEPHALIC VEIN

Before discussing the lateral anastomotic mesencephalic vein as seen during the venous phases of carotid angiography, a description of the normal great anterior cerebellar vein is in order since the anterior portion of this vessel is included in the anomalous vein. The great anterior cerebellar vein has not been described in detail in the literature on cerebral angiography although it is clearly indicated in a sketch by Greitz and Lindgren.[3] In this illustration, this vein is referred to as the anterior superior cerebellar vein. While this vessel is frequently incomplete or segmented, it may exist as a channel of uniform caliber extending from the great vein of Galen to the superior petrosal sinus (Fig. 1, *A–D*). From its junction with the great vein of Galen, the great anterior cerebellar vein runs forwards, downwards and laterally in the cisterna ambiens approximately paralleling the margin of the tentorium and the anterior cerebellar notch. In this portion of its course, the central lobule of the cerebellum and its lateral wing are located on its lateral aspect while medially it is in relationship to the tectum and tegmentum of the mid-brain. Near the anterior margin of the cerebellar notch, the vessel may run medially for a short distance to reach the lateral sulcus of the mid-brain or the prolongation of this sulcus downwards on the lateral aspect of the pons. The vein then continues downwards and laterally along the superior or

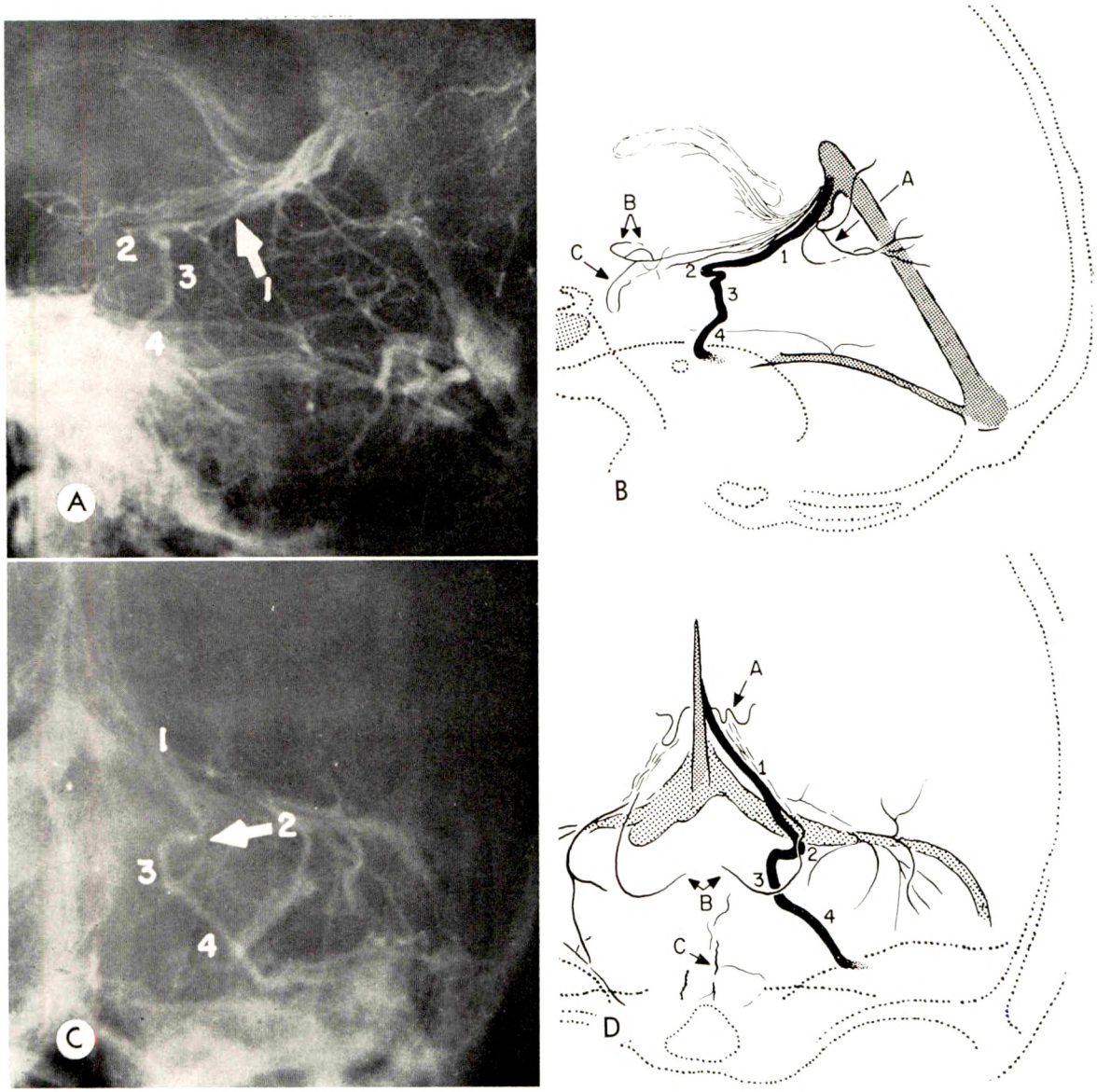


Fig. 1. The great anterior cerebellar vein; venous phase of vertebral angiography.

(*A*) Lateral projection. The great anterior cerebellar vein is seen as a continuous channel extending from the great vein of Galen to the region of the internal auditory meatus. Two main portions, a horizontal or superior part (arrow, segment 1) and a vertical or anterior part (segments 3 and 4) can be distinguished. In most patients, these two portions are separate vessels, a superior and an anterior cerebellar vein. In this patient, a short anastomotic channel (segment 2) connects these two parts. Segments 3 and 4 are incorporated into the lateral anastomotic mesencephalic vein in instances in which this anomaly is present. In such cases, segment 1 remains as a separate anterior superior cerebellar vein which drains backwards into the great vein of Galen.

(*B*) Diagram of *A*. Internal occipital veins (arrow A), interpeduncular (arrow B), and prepontine veins (arrow C) are also illustrated.

(*C*) Anteroposterior semi-axial projection in the same patient. Segment 1 runs along the anterior cerebellar notch near the edge of the tentorium. Segment 2 extends medially for a short distance to the lateral pontine sulcus. Segment 3 runs inferiorly in this sulcus. Segment 4 extends laterally and downwards on the anterior aspect of the cerebellum to join veins in the region of the internal auditory meatus and the superior petrosal sinus.

(*D*) Diagram of *C*. Internal occipital veins (arrow A), interpeduncular (arrow B), and prepontine veins (arrow C) are also illustrated.

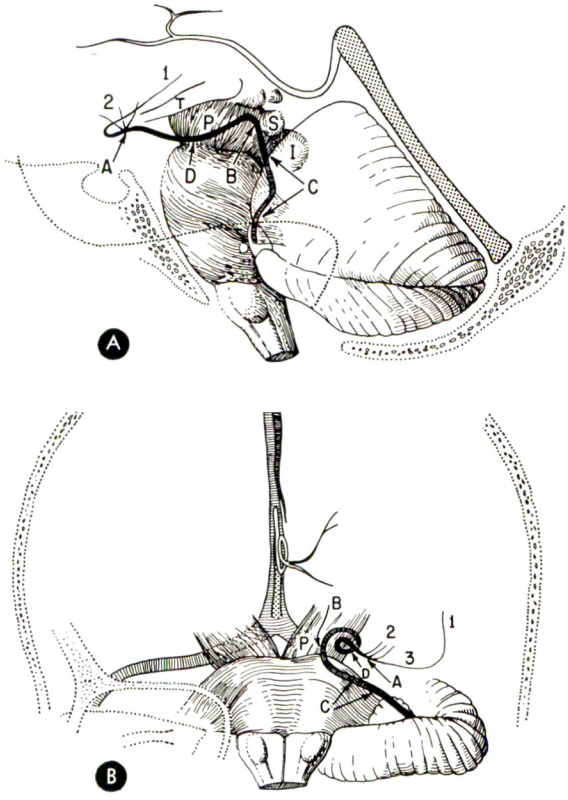


FIG. 2. Diagrammatic representation of the lateral anastomotic mesencephalic vein.
(*A*) Lateral projection. Insula (1) and inferior striate veins (2) join to form the anterior end (arrow A) of the lateral anastomotic mesencephalic vein. The vessel then extends backwards in a smooth curve convex inferiorly (arrow D) below the optic tract (T) and around the cerebral peduncle (P). At the posterior margin of the peduncle, *i.e.*, the lateral mesencephalic sulcus, the vein turns (arrow B) and descends between the pons and cerebellum (arrows C) to the level of the flocculus or internal auditory meatus. S and I mark the superior and inferior colliculi. The portion of the vessel covered by the cerebellum is indicated in hatched fashion. (*B*) Anteroposterior projection. Insula (1) and inferior striate veins (2) join the deep middle cerebral vein (3) which empties into the anterior end (arrow A) of the lateral anastomotic mesencephalic vein. The anterior portion of the vein is seen "on end" and forms a loop (arrow D) as it runs backward. The vessel turns around the peduncle to reach the lateral mesencephalic sulcus (arrow B) and then runs downwards and laterally (arrows C) anterior to the brachium pontis and in the horizontal fissure of the cerebellum to the region of the flocculus and internal auditory meatus. The portion of the vein behind the peduncle and pons is indicated in hatched fashion.

anterior aspect of the brachium pontis to the region of the flocculus or cerebellopontine angle. In its oblique course anterior to the cerebellum, this vein is located in the anterior part of the great horizontal fissure of the cerebellum. It is the portion of the great anterior cerebellar vein between the lateral sulcus and the superior petrosal sinus which is incorporated into the lateral anastomotic mesencephalic vein when this vessel is present.

The typical appearance and anatomic relationships of the lateral anastomotic mesencephalic vein are diagrammatically illustrated in Figure 2, *A* and *B*. From the roentgen point of view, the feature which usually leads to a search for anomalous drainage of the basal vein is recognition of the absence of the normal posterior extension of the basal vein into the internal cerebral vein (Fig. 3, *A–D*). The absence of this segment is evident in both the lateral and anteroposterior projections. The basal vein should always be seen if serial roentgenograms are taken, *e.g.*, at the rate of one per second in the venous phases. The anterior horizontal portion of the basal vein can be recognized by identification of the anterior deep venous tributaries which unite to form the origin of this vessel. These tributaries include the inferior striate veins, the insula and orbital veins and the deep middle cerebral vein. These vessels form a radiating pattern, the center of which is related to the anterior end of the basal vein. While these tributaries are ordinarily best seen in the lateral projection, they can usually also be identified at least faintly or partly in the anteroposterior projection and serve the same purpose. In the anteroposterior projection, however, the anterior or horizontal portion of the basal vein is usually seen "on end" and shows an irregular or looped configuration, the components of which are difficult to identify. In the lateral view, this portion of the basal vein is seen with little difficulty. In those instances in which a lateral anastomotic mesencephalic vein is present, as the basal vein is followed posteriorly, an acute

change in direction occurs—the vessel turns rather abruptly inferiorly. The junction of the horizontal and vertical portions, the knee, is at a point about 2.5 to 3 cm. behind and a short distance above the posterior clinoids. This point corresponds to the position of the lateral mesencephalic sulcus or posterior margin of the cerebral

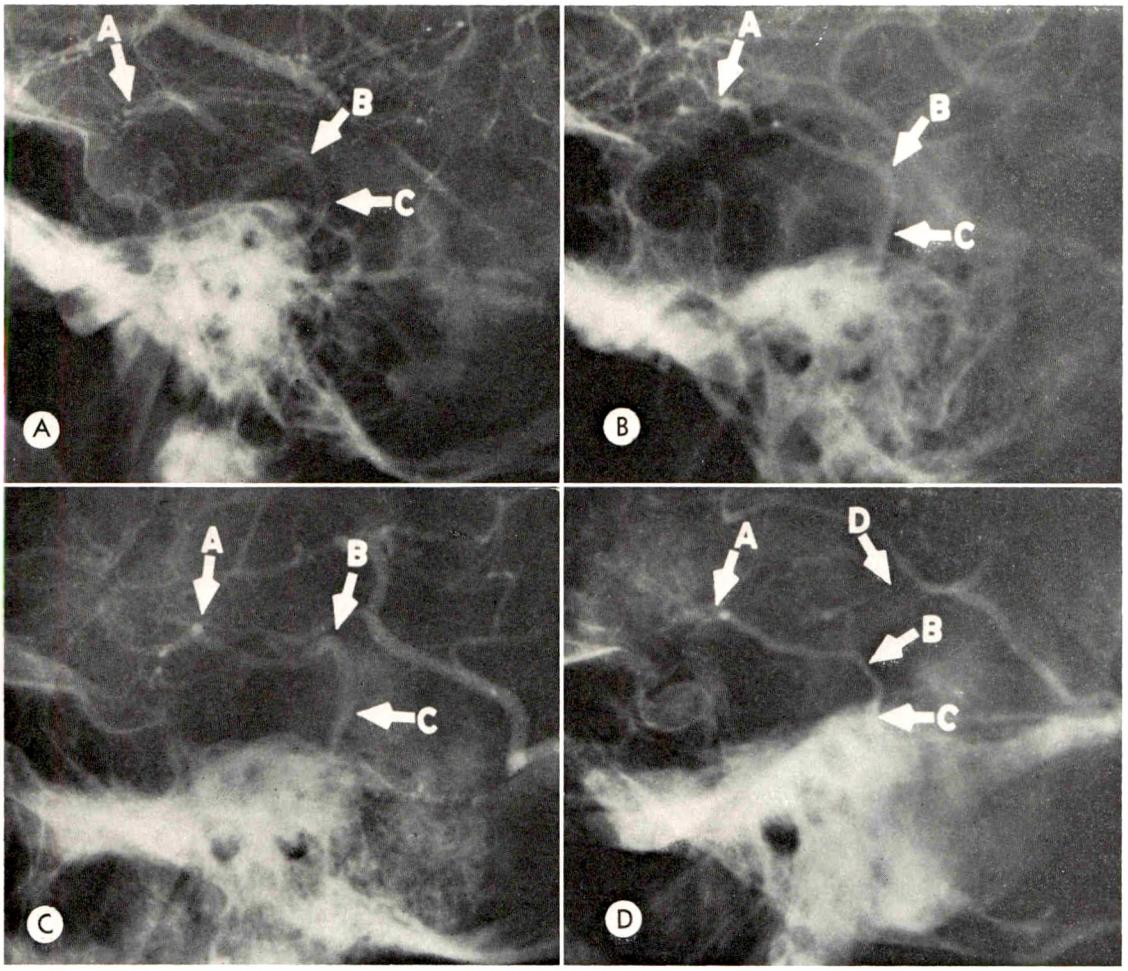


Fig. 3. The lateral anastomotic mesencephalic vein as seen during the venous phases of carotid angiography in 4 different patients. The vessel is composed of two portions—a horizontal anterior part (segment A–B) and a vertical posterior part (segment C). The anterior part represents the anterior portion of the basal vein. The posterior part of the normal basal vein is absent. Instead, the anterior part continues in a descending fashion along the lateral aspect of the brain stem and the anterior surface of the cerebellum. The point B or knee corresponds to the location of the lateral mesencephalic sulcus or posterior border of the cerebral peduncle.

(*A*) The knee (arrow B) is gently curved and the descending segment (arrow C) is rather markedly convex posteriorly. Arrow A points to the transverse portion of the deep middle cerebral vein a short distance in front of the fine radiating inferior striate veins ("star-shaped" pattern).

(*B*) The knee (arrow B) is abrupt and forms almost a right angle. The descending limb (segment C) is straight.

(*C*) The transverse or basal portion (segment A–B) is gently looped inferiorly. The knee (arrow B) shows an acute angulation directed superiorly.

(*D*) The knee (arrow B) is low in position. The anterior portion (segment A–B) runs downwards as well as backwards. The inferior ventricular vein (arrow D) joins the lateral anastomotic mesencephalic vein anterior to the knee via a short vertical trunk.

peduncle. The horizontal portion of the vein corresponds rather closely to the anterior portion of a normal basal vein but frequently is at a somewhat lower level as it runs posteriorly. The knee may be smoothly convex or more acutely angulated. As the vessel runs downwards, it is usually somewhat convex posteriorly. The combined vein forms a single channel of rather uniform caliber. In the anteroposterior projection (Fig. 4, *A–D*), the vertical or descending limb of the lateral anastomotic mesenteric vein presents as an oblique channel extending downwards and laterally from the knee about 1.5 cm. lateral to the mid-line to the level of the

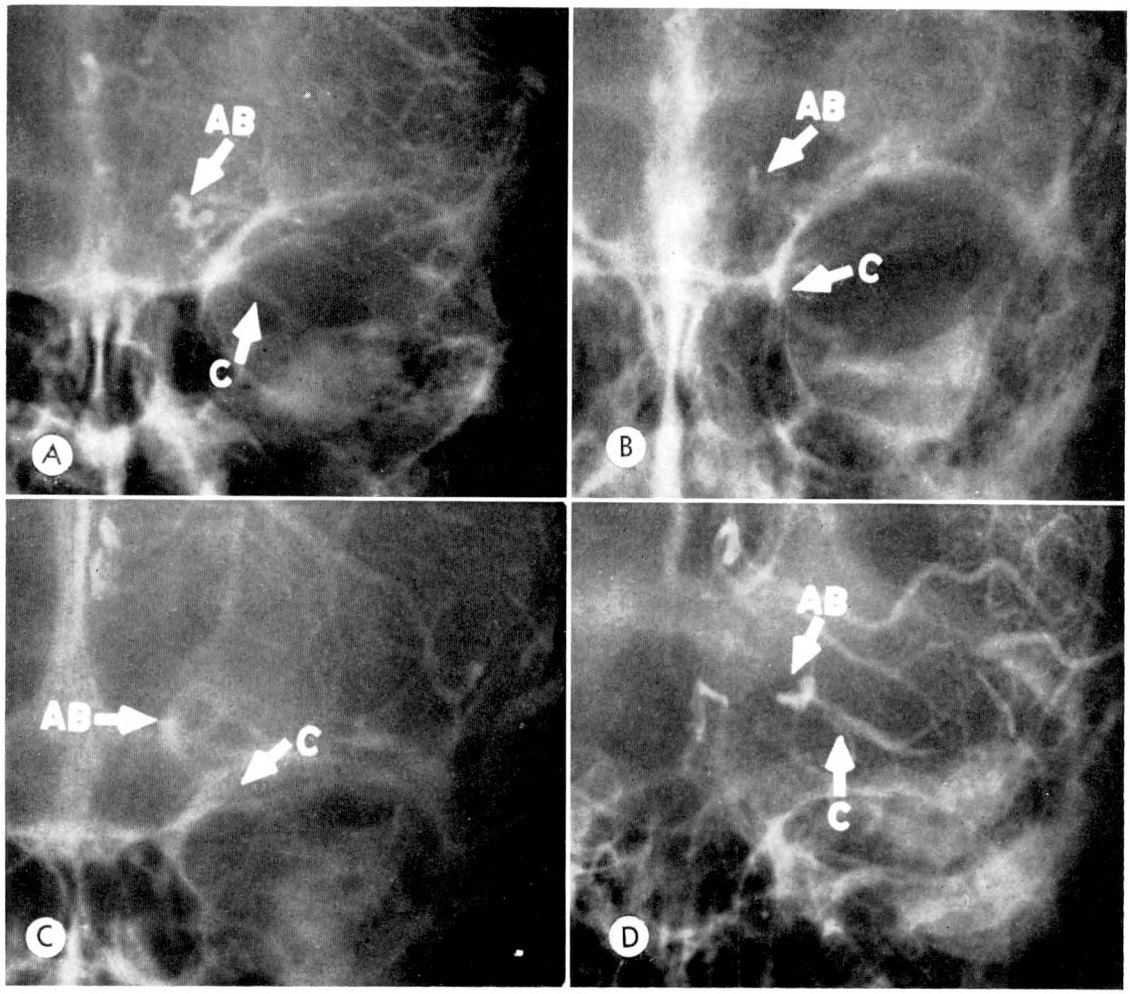


FIG. 4. The lateral anastomotic mesencephalic vein in the anteroposterior projection in 4 different cases. These are the same patients illustrated in Figure 3. The anterior basal portion of the vein is seen "on end" (arrow AB). The descending limb (arrow C) runs downwards and laterally to the region of the internal auditory meatus or the superior border of the petrous pyramid.

(*A*) The anterior portion (arrow AB) forms a tight loop in this projection. The descending portion (arrow C) is quite straight.

(*B*) The descending limb (arrow C) is rather markedly convex medially.

(*C*) The descending limb (arrow C) is straight and extends to the superior margin of the petrous pyramid lateral to the internal auditory meatus.

(*D*) The descending limb (arrow C) extends rather far laterally. It is partially overlapped by the transverse portion of the deep middle cerebral vein.

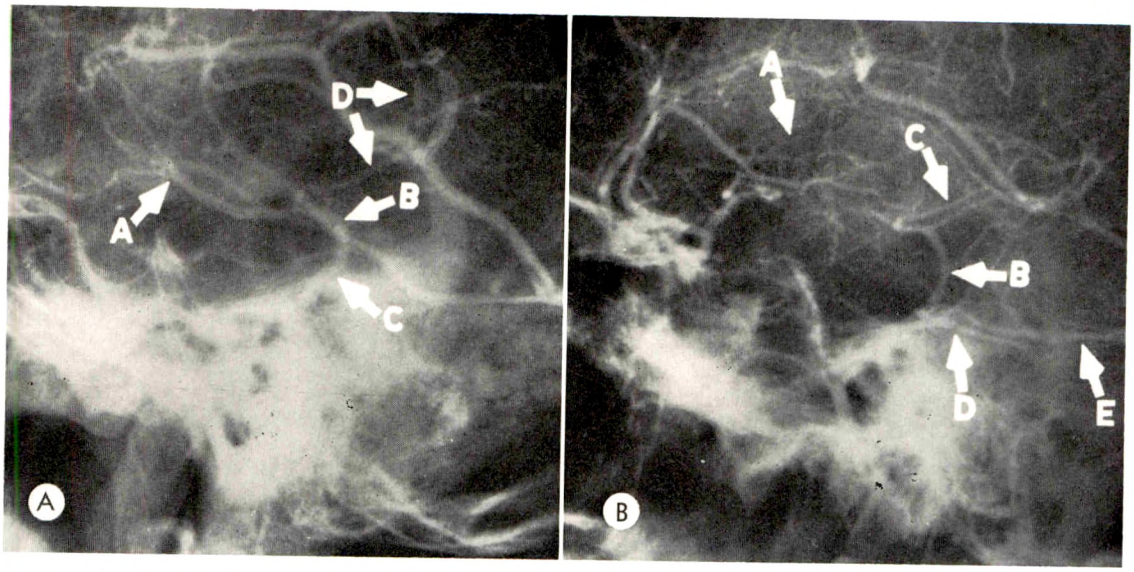


Fig. 5. (*A*) The lateral anastomotic mesencephalic vein (arrows A, B, C) is well seen. A large inferior ventricular vein (arrow D) joins the basal portion of this vessel at the usual point a short distance anterior to knee. This appearance of the inferior ventricular vein is more characteristic than the example shown in Figure 3*D*.

(*B*) In this patient, on multiple roentgenograms of the venous phases of carotid angiography, there was no evidence of a normal basal vein. The anterior deep venous tributaries, which ordinarily join to form the basal vein (arrow A), drain into the sylvian system of vessels. The descending limb of the lateral mesencephalic vein (arrow B) has a characteristic appearance and location. Moreover, the inferior ventricular vein (arrow C), which appears to be double, joins this vessel at the usual site. In this patient, the lateral mesencephalic vein enters directly into the superior petrosal sinus (arrow D). There is an additional tentorial channel (arrow E) which drains an inferior cortical temporal vessel.

internal auditory meatus. The exact position and configuration of this channel in the anteroposterior projection is somewhat variable. It may be quite straight or it may be arched with convexity directed medially. The termination of the vein in the superior petrosal sinus is usually obscured by the petrous pyramid and by dilution with unopacified blood from the floccular veins or veins of the cerebellopontine angle ("petrosal veins"). In some cases, however, the anastomotic vein joins the superior petrosal sinus directly and this sinus may also be opacified (Fig. 5*B*).

While the configuration of the lateral anastomotic mesencephalic vein in both the lateral and anteroposterior projections is sufficiently characteristic to permit recognition, the vessel may be obscured by one or more other veins. In the lateral projection, there often is a superficial temporal vein which may show a similar configuration. This vessel, however, receives superficial tributaries and empties into the transverse sinus. In the anteroposterior projection, an anterior cortical superficial vein may have a somewhat similar course to the vertical limb of the mesencephalic vein. The recognition of typical cortical tributaries and the fact that it extends to the mid-line to join the superior longitudinal sinus permit differentiation. In the anteroposterior projection, the transverse portion of the deep middle cerebral vein may simulate or partially overlap the lateral anastomotic mesencephalic vein (Fig. 4*D*). The inferior striate veins and the insula veins which join the deep middle cerebral vein can, however, frequently be recognized and serve to identify the deep middle cerebral vein.

As pointed out above, the horizontal por-

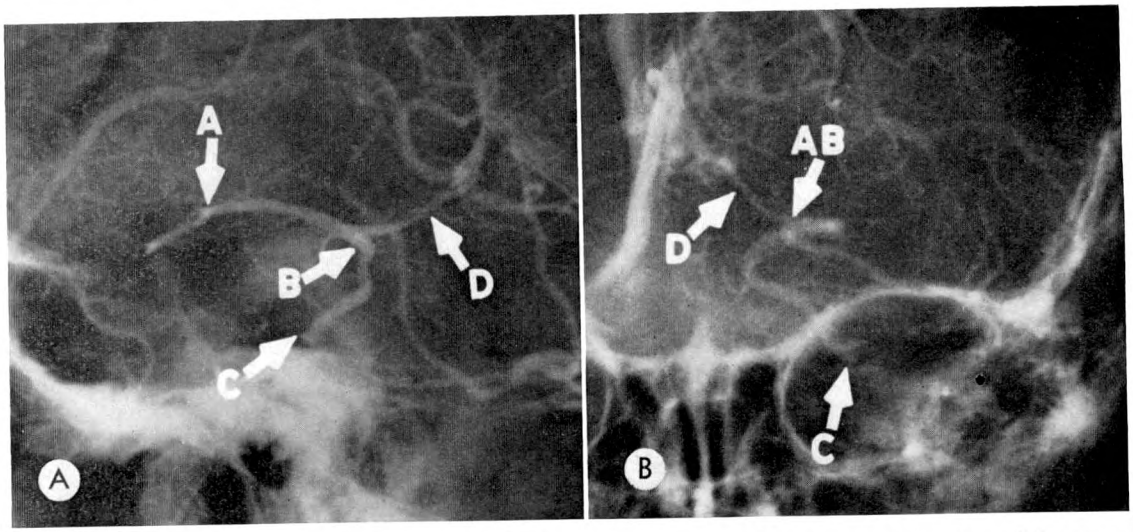


FIG. 6. An unusual example of the presence of both the lateral anastomotic mesencephalic vein and the posterior portion of the basal vein.

(*A*) In the lateral projection, the typical two components (segment A–B and segment B–C) of the lateral anastomotic mesencephalic vein are well seen. Arrow D points to a vessel which has the typical appearance and location of the posterior portion of a normal basal vein emptying into the great vein of Galen. Incidentally, note the close resemblance of the descending limb of the lateral anastomotic mesencephalic vein in this patient to the appearance of the descending limb of the greater anterior cerebellar vein in Figures 1, *A* and *B*.

(*B*) The presence of both the lateral anastomotic mesencephalic vein and the posterior portion of the basal vein is confirmed in the anteroposterior projection. The "end on" appearance of the anterior portion of the anastomotic vessel (arrow AB) and the termination of the descending limb at the upper pole of the petrous pyramid (arrow C) are typical. The appearance and position of the posterior portion of the basal vein (arrow D) are characteristic.

tion of the lateral anastomotic mesencephalic vein represents the normal anterior part of the basal vein. The anterior deep venous tributaries of both are identical. This is also true of another normal tributary of the basal vein—the inferior ventricular vein (Fig. 5*A*) which runs downwards and forwards in the temporal horn to join the basal vein at the anterior end of the choroidal fissure. This vein has a characteristic arcuate appearance as well as location. From our present point of view, it can also be used to identify the lateral anastomotic mesencephalic vein particularly in those instances in which the basal vein as such is completely absent (Fig. 5*B*). In such cases, the anterior deep veins drain into the middle cerebral and superficial sylvian system of vessels while the inferior ventricular vein joins the anastomotic mesencephalic vein. It might be noted also that in a rare instance, despite the presence of a lateral anastomotic mesencephalic vein, the normal posterior extension of the basal vein into the great vein of Galen may also be present (Fig. 6, *A* and *B*). This combination, however, appears to be uncommon.

In cases of anomalous drainage of the basal vein via pial vessels into the pontine plexus, tortuous vessels are seen in the region of the chiasmatic and interpeduncular cisterns which extend into the posterior fossa a short distance behind and lateral to the dorsum sellae (Fig. 7, *A* and *B*). In these instances, no large single continuous anastomotic channel is present. The posterior portion of the basal vein may (Fig. 7*A*) or may not (Fig. 7*B*) be evident. Angiographically, this variety is difficult to delineate in detail because the vessels are relatively small and a full study would re-

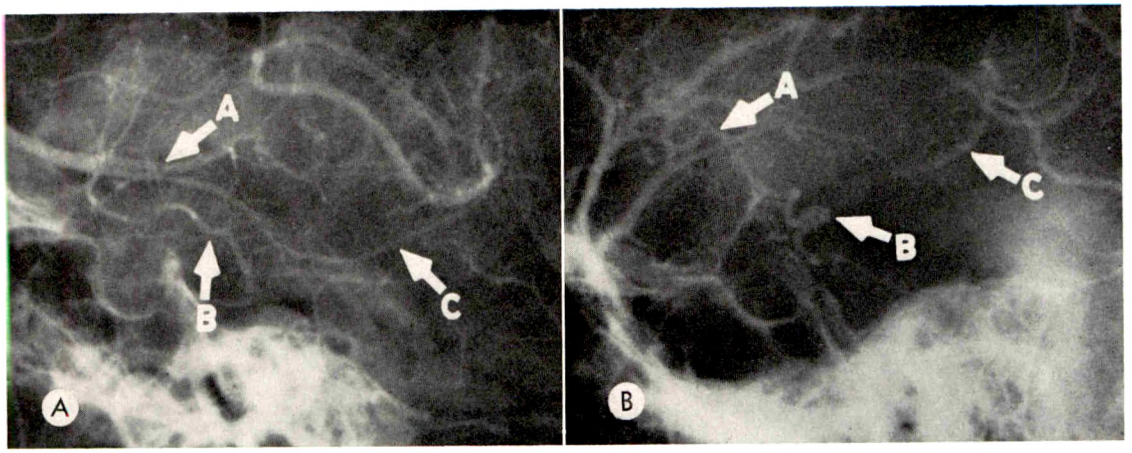


Fig. 7. (*A*) In this patient, a small posterior portion of the normal basal vein is present (arrow C). There is however, no normal anterior portion. Instead, inferior striate veins (arrow A) drain into a tortuous channe (arrow B) which extends backwards and downwards to the lateral aspect of the pons. The further course of this channel is not evident presumably because of dilution with nonopacified blood from veins of the posterior fossa.
(*B*) In another patient, the inferior striate veins (arrow A) drain into a tortuous vessel which extends downwards and backwards into the posterior fossa (arrow B). There is no evidence of a normal basal vein. The inferior ventricular vein (arrow C) is seen but the method of drainage of this vessel is not evident.

quire both carotid and vertebral angiography. From a surgical point of view, however, these vessels may be of importance because of the fact that they bridge the middle and posterior fossa and may require careful attention during dissections in the region of the cerebellopontine angle.

Anomalous Drainage of the Basal Cerebral Vein via the Channel in the Tentorium

The second main group of anomalous drainage of the basal vein, that is, via the channel in the tentorium, does not have a unique roentgen appearance since the tentorial channel may be located either in the

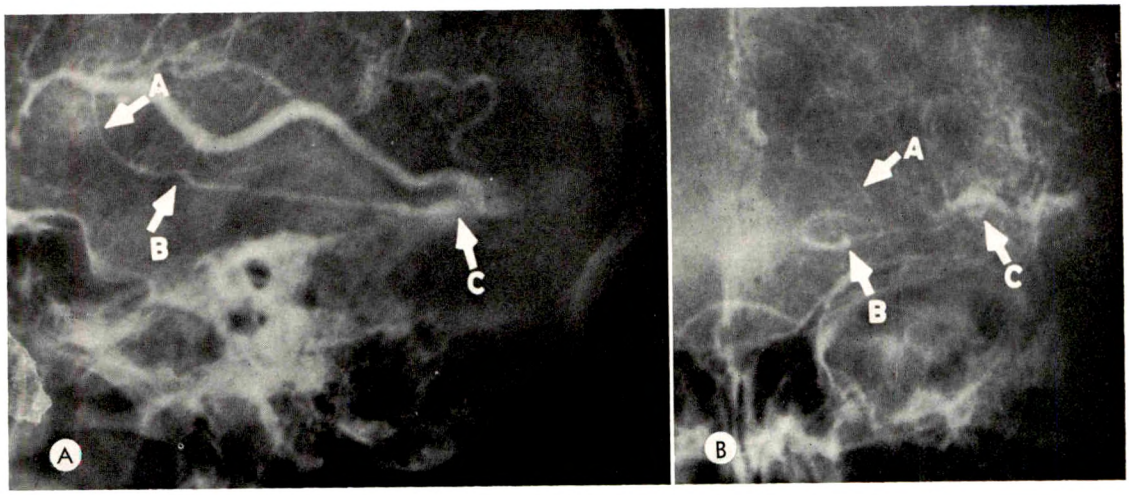


Fig. 8. Anomalous basal venous drainage via a tentorial channel into the lateral sinus.
(*A*) A large inferior striate vein (arrow A) runs into the basal vein which enters the dura (arrow B) and continues as a tentorial channel into the lateral sinus (arrow C).
(*B*) The inferior striate vein (arrow A) enters the basal vein (arrow B) which loops medially and then runs laterally into the tentorium to reach the lateral sinus (arrow C).

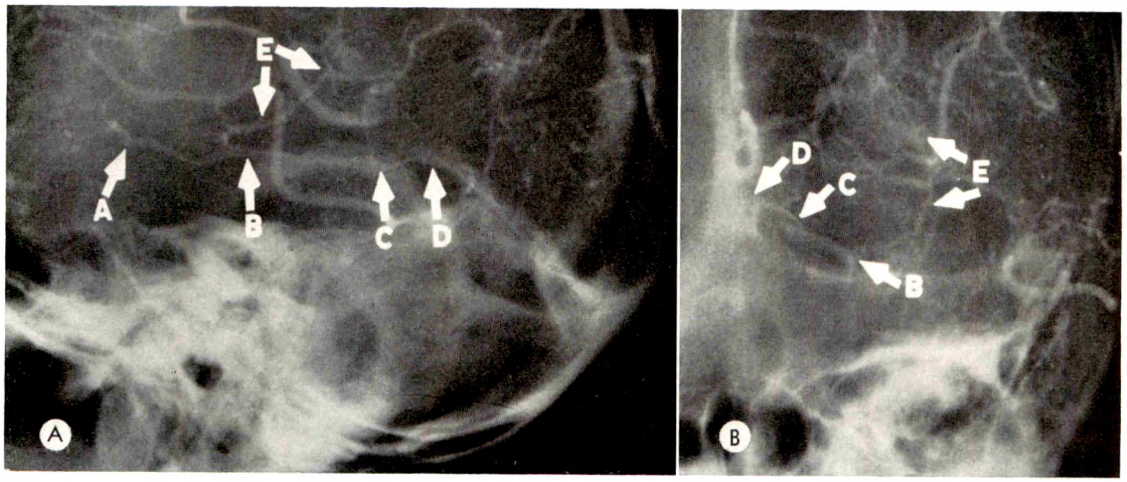


FIG. 9. Anomalous drainage of the basal vein via a tentorial channel into the straight sinus.

(*A*) The anterior portion of the basal vein (arrow A–arrow B) is not remarkable. However, the vein does not extend backwards in normal fashion but enters a channel in the tentorium (arrows B, C, D) which empties into the straight sinus. The tentorial portion begins near arrow B and shows a change in course at arrow C. The inferior ventricular vein (arrow E) has a characteristic location and appearance and drains into the anomalous basal channel.

(*B*) In the anteroposterior projection, the inferior ventricular vein (arrow E) joins the basal vein at its usual location (arrow B). The tentorial portion of this vessel is composed of two parts, segment B–C and segment C–D. There is a suggestion in both the anteroposterior and lateral projections that the vein may parallel the straight sinus for some distance before it actually enters it.

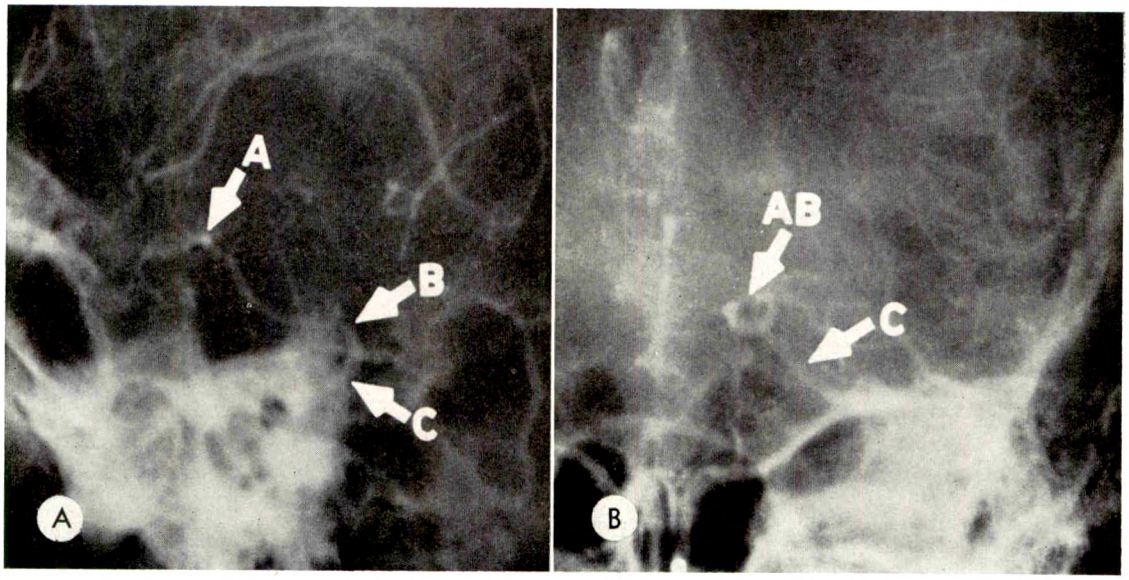


FIG. 10. Tumor in the thalamic region.

(*A*) In the lateral projection, the lateral mesencephalic vein (arrows A, B, C) replaces the normal basal vein. The knee (arrow B) is low in position and the descending segment (arrow C) is short and markedly convex posteriorly. The anterior segment (arrow A–arrow B) is looped markedly inferiorly. The internal cerebral vein is bowed superiorly by the tumor.

(*B*) In the anteroposterior projection, there is no remarkable deformity of the lateral anastomotic mesencephalic vein (arrows AB, C). However, the medial upper portion of this vein may be located somewhat closer to the mid-line than is ordinarily seen.

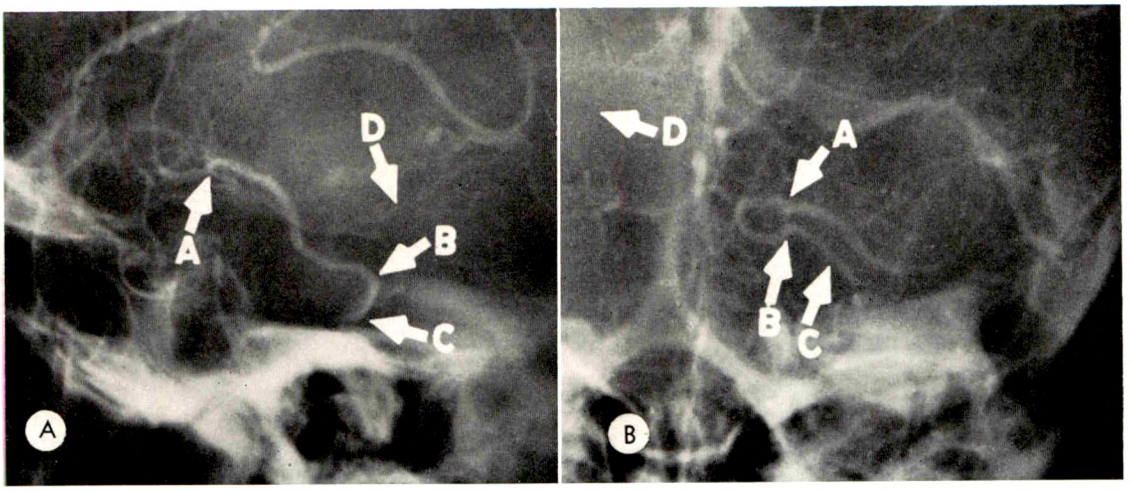


Fig. 11. Large neoplasm in the temporoparietal region.
(*A*) In the lateral projection, the lateral anastomotic mesencephalic vein (arrows A, B, C) replaces the normal basal vein. The posterior portion of the horizontal limb and the knee are displaced downwards. The basal vein of the opposite side (arrow D) is faintly seen.
(*B*) In the anteroposterior projection, a long circuitous channel is evident, composed of the deep middle cerebral vein and the lateral anastomotic mesencephalic vein. Arrow A indicates the junction of the deep middle cerebral vein with the anterior end of the horizontal limb of the mesencephalic vein. The posterior end (arrow B) of this vein is at a lower level than its anterior end. Segment A–B appears to be displaced medially. The descending limb (arrow C) shows a marked convexity laterally. The basal vein of the opposite side (arrow D) is faintly seen.

medial or lateral portions of the tentorium and empty into the straight or into the transverse sinus. When the vessel extends laterally (Fig. 8, *A* and *B*), a rather bizarre appearance of a long straight channel running from the region of the anterior perforated space posteriorly and laterally may be seen. It is ordinarily not possible to determine at exactly what point the vessel becomes incorporated in the dura of the tentorium. The entrance of this vessel into the transverse sinus may occur at any point from the torcula to a point posterior to the sigmoid sinus. In those instances in which the tentorial channel enters the straight sinus (Fig. 9, *A* and *B*), the course in the tentorium is at a higher level and more circuitous.

DISCUSSION

The usefulness of the lateral anastomotic mesencephalic vein and the other variations in the basal vein in the identification and localization of cerebral lesions has not been fully explored. In several instances (Fig. 10, *A* and *B*, and 11, *A* and *B*), there has been obvious deformity and downward displacement of the knee and of the horizontal portion of the anastomotic mesencephalic vein in the presence of supratentorial tumors presumably with downward tentorial herniation. The fact that the upper portion of the vertical limb of this vessel identifies the lateral mesencephalic sulcus should be of diagnostic importance with tumors or displacements in this area but further investigation will be required to demonstrate this. At any rate, the recognition of normal variants in basal vein drainage may help in preventing diagnostic errors and furnish useful landmarks for identifying specific cerebral structures.

SUMMARY

The basal cerebral vein of man represents a late secondary anastomotic channel derived from several primitive vessels. Failure of fusion of these vessels and persistence of more embryonic pathways result in rather frequent normal variations of this vessel.

The most common and most characteristic of these variations is the lateral anastomotic mesencephalic vein of Padget. This vessel is described in detail. Other variations including abnormal drainage into the pontine plexus and into the transverse and straight sinuses via a tentorial channel are also illustrated.

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CLINICAL EVALUATION OF TWO NEW CONTRAST MEDIA: CONRAY AND ANGIO-CONRAY*

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THIS study was undertaken to determine the advantages and usefulness of Conray and Angio-Conray, two new contrast media based on 5-acetamido-N-methyl-2,4,6-triiodoisophthalamic acid (iothalamic acid). Iothalamic acid is a white crystalline solid with a molecular weight of 614 and an iodine content of 62 per cent. It is essentially an isomer of sodium diatrizoate with an identical iodine content and molecular weight. Conray is a 60 per cent solution of meglumine iothalamate and Angio-Conray is an 80 per cent solution of sodium iothalamate.

Conray has an iodine content of 28 per cent with a viscosity of 6.1 centipoise at 25° C. and 4.0 centipoise at 37.5° C. Angio-Conray has an iodine content of 48 per cent with a viscosity of 14.4 centipoise at 25° C. and 8.4 centipoise at 37.5° C. (Table I). Iothalamic acid was the 216th compound synthesized by Mallinckrodt Pharmaceuticals in the search for a new and better compound.

The development of more suitable opaque media has been hampered by the lack of guiding principles concerning the relationship of chemical structure to such properties as solubility, toxicity, and mode of elimination from the human body.

We have progressed from aliphatic compounds, such as methiodal with a single molecule of iodine, to cyclic compounds with two iodine molecules. With the synthesis of aromatic compounds, three iodine molecules became possible. It was found that with the presence of an acetylamino group in the 5 position of the benzene ring or when the ring was completely filled, the compound would have a lower toxicity. In iothalamic acid, one of the acetylamino groups was changed to a methyl-carbamoyl group. This change produced an isophthalic acid derivative rather than a benzoic acid derivative such as sodium diatrizoate and accounts for the increased solubility, lower viscosity, and lower toxicity of iothalamic acid. The chemical structures of some of the early and present opaque media are given in Table II. The chemical structure of iothalamic acid is also given.

The intravenous LD_{50} (mice) for Conray is 17,000 mg./kg. and for sodium diatrizoate 50 per cent it is 14,000 mg./kg.; the intravenous LD_{50} (rats) for Conray is 20,000 mg./kg. and for sodium diatrizoate 50 per cent 11,400 mg./kg.; the intracerebral LD_{50} (rabbits) for Conray is 78 mg./kg. and for sodium diatrizoate 50 per cent 8.4 mg./kg.[3,5] These toxicity studies are presented in an outline form in Table III.

Blood-brain-barrier studies in dogs demonstrated that Conray was superior to sodium diatrizoate 50 per cent.[2] Excretion studies in dogs using the cross-over technique showed that the degree of visualization of the kidney and ureters was comparable with sodium diatrizoate 50 per

TABLE I

Product	Iodine Content (per cent)	Viscosity (cps)	
		25° C	37.5° C
Conray Brand of Meglumine Iothalamate 60%	28	6.1	4.0
Angio-Conray Brand of Sodium Iothalamate 80%	48	14.4	8.4

* From the Department of Radiology, University of Louisville School of Medicine, Louisville, Kentucky.
Aided in part by a grant from Mallinckrodt Chemical Works.

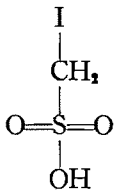
cent. With intravenous administration to anesthetized dogs, the electrocardiographic pattern was normal from 100 to 4,000 mg./kg.[5]

Two unanesthetized dogs received 5,000 mg./kg. intravenously of meglumine iothalamate 60 per cent and 2 others were given doses of 10,000 mg./kg. All the dogs

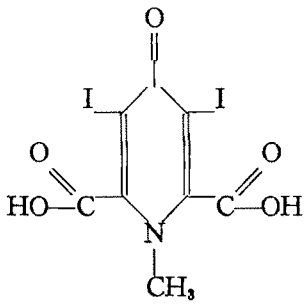
TABLE II

CHEMICAL STRUCTURES

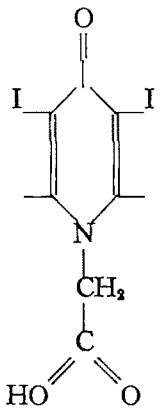
Methiodal (Skiodan)



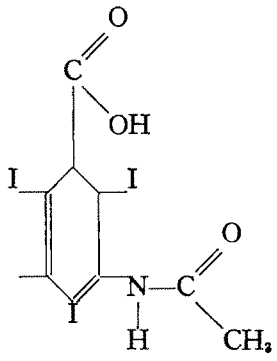
Iodomethamate (Uroselectan)



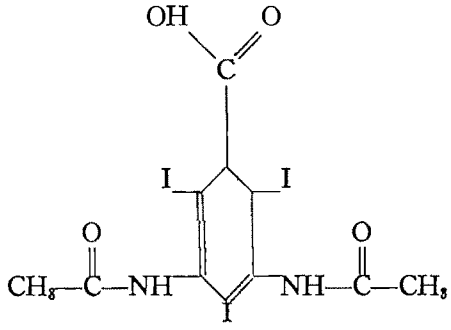
Iodopyracet (Diodrast)



Acetrizoate (Urokon)



Diatrizoate (Hypaque)



Iothalamate (Conray)

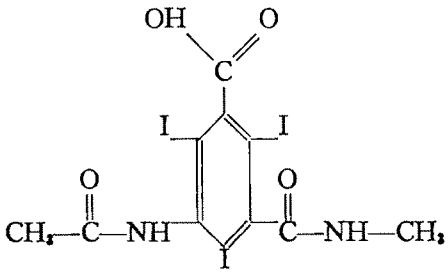


Table III

PHARMACOLOGIC STUDIES

Acute Toxicity	Meglumine Iothalamate 60% (Conray)[5]	Sodium Diatrizoate 50%[3]
(a) Intravenous LD_{50} (mice)	17,000 mg./kg. (16,000–18,000)	14,000 mg./kg. (13,200–14,800)
(b) Intravenous LD_{50} (rats)	20,000 mg./kg. (17,900–22,400)	11,400 mg./kg. (10,700–12,100)
(c) Intracerebral LD_{50} (rabbits)	78 mg./kg.	8.4 mg./kg. (6.2–10.6)

showed some retching, and defecation occurred with one dog at the 5,000 mg./kg. level. At autopsy, all organs of the 2 dogs receiving 5,000 mg./kg. and one dog at 10,000 mg./kg. were within normal limits. The other dog at the 10,000 mg./kg. level injured himself physically during the observation period and meaningful pathology data were unobtainable.

Ten dogs received repeated daily intravenous doses of meglumine iothalamate 60 per cent at levels of 4,000 to 6,000 mg./kg. and sodium iothalamate 80 per cent at a level of 500 mg./kg. Both salts of iothalamate were well tolerated by the dogs and the only difference observed in comparison to the control dogs receiving sterile physiologic saline was the occurrence of some vomiting among the dogs which received the 4,000 to 6,000 mg./kg. daily dosage level of meglumine iothalamate 60 per cent. There was no vomiting among the dogs receiving 80 per cent sodium iothalamate. Results of the hematologic determination, biochemical studies, urinalysis, and gross and microscopic pathologic evaluations were essentially normal and comparable to the control dogs.[5]

According to Bernstein *et al.*,[1] the renal and spinal cord tolerance of Angio-Conray in dogs indicates that Angio-Conray is at least as safe as the diatrizoates and is probably safer.

Table IV shows the comparison of the

Table IV

COMPARISON OF COMMON CONTRAST MEDIA

	Conray	Angio-Conray	Ditriokon	Hypaque M 75%	Cardiografin	Urokon Sodium 70%
Chemical Nature	60% aqueous solution of meglumine iothalamate	80% aqueous solution of sodium iothalamate	31.4% sodium diprotrizoate (miokon sodium) and 36.7% sodium diatrizoate (hypaque sodium) in aqueous solution; a mixture	25% sodium diatrizoate and 50% N-methyl glucamine diatrizoate in aqueous solution; a mixture	85% aqueous solution of N-methyl glucamine diatrizoate	70% aqueous solution of sodium acetrizoate
Relative Viscosity (in cps with H_2O as unity)	25° C 6.1 37.5° C 4.0	25° C 14.4 37.5° C 8.4	25° C 8.4 37.5° C 5.5	37.5° C 11.0	25° C 28.8 37.5° C 23.3	25° C 7.2 37.5° C 6.1
Iodine Content	28% w/v	48% w/v	40% w/v	38.3% w/v	40% w/v	46% w/v
Appearance	Clear, aqueous solution	Clear, aqueous solution	Clear, aqueous solution	Clear, aqueous solution	Clear, moderately viscid solution	Clear, aqueous solution
LD_{50} mg./kg. in Mice (Manufacturer's figures)	17,000±1,000	19,000	10,700	12,600±877	10,500	8,000 to 11,200

properties of Conray and Angio-Conray with some of the more common contrast media.

CLINICAL STUDIES

Intravenous urography with Conray has been performed on 665 patients using 20 cc. (adult) doses with appropriate adjustments in the case of infants and children. It appears that the compound is more rapidly excreted than the other common opaque media and maximum density of contrast is evident in 5 minutes (Fig. 1). This probably accounts for the greater density of these pyelograms when compared with those using opaque media with similar iodine content. The incidence of side effects is less than when urokon 70 per cent, hypaque 50 per cent or renovist are used. All persons who injected the compound were impressed with the fewer side effects. One advantage was the lack of sticking of the barrel of the syringe. One person in the series developed generalized urticaria which disappeared rapidly after the administration of 10 mg. of benadryl intravenously. Because of the rapid excretion and density of Conray, a new exposure program was used which consists of a scout roentgenogram, a 5 minute anteroposterior roentgenogram, followed in rapid order by a posteroanterior and an upright roentgenogram. The entire examination is completed in 10 minutes. Delayed roentgenograms are taken when needed. The posteroanterior roentgenogram shows excellent filling of the ureters and better visualization of the anterior bladder wall. This does away with the need for compression which is a troublesome and often useless procedure.

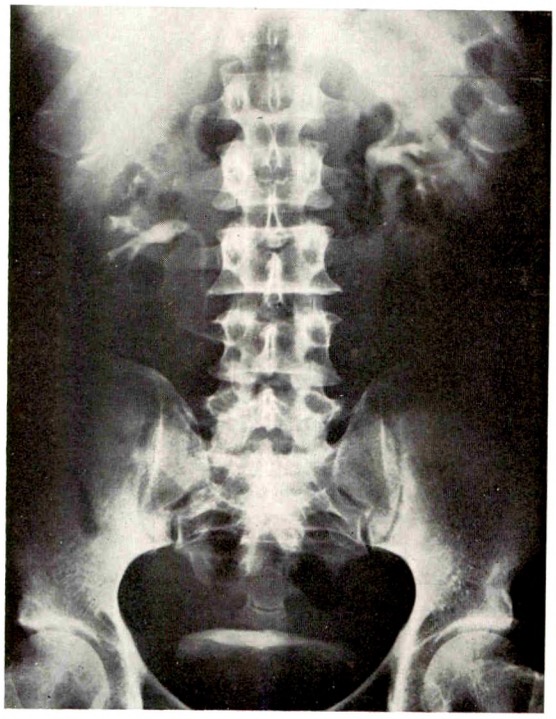


FIG. 1. Excretory urogram with 60 per cent meglumine iothalamate. Normal examination in a 45 year old male showing rapid excretion of the opaque medium at 5 minutes. In our series of 665 patients, the maximum opacification occurred at 5 minutes.

The injection time of the opaque medium was usually 1 to 3 minutes. Longer injection times (5–10 minutes) were compared to shorter injection times (1–3 minutes) in 300 patients and there were no differences in the incidence of side effects. It is felt unnecessary to use an injection time longer than 1 to 3 minutes. For example, in angiography the opaque medium is usually injected rapidly with pressure and in larger amounts and there is no increased incidence of reactions. Table V presents the number of patients and number of injections in our series.

In cerebral angiography, direct carotid injection of Conray has been well tolerated and visualization has been superior to other opaque media in 210 patients with a total of 1,600 single injections. The average dose employed has been 8 cc. per injection with 4 to 5 injections per side (Fig. 2).

The exposure time is a few seconds earlier than with sodium diatrizoate 50 per cent. Comparison of the roentgenographic density of Conray with sodium diatrizoate 50 per cent in 150 patients demonstrated a greater density of Conray. There seemed to be a better cerebral tolerance using Conray and no appreciable side effects were noted.

Aortocaroticocerebral angiography is a

TABLE V

CLINICAL EVALUATION OF CONRAY AND ANGIO-CONRAY

	Injections	Examinations
I. *Excretory Urography*	665	665
II. *Cerebral Angiography*	1,600	210
(a) Aortocaroticocerebral	35	18
III. *Abdominal Angiography*		
(a) Percutaneous Femoral Arteriography	45	35
(b) Intravenous Aortography	7	4
IV. *Cardiovascular Visualization*		
(a) Thoracic Aorta, Selective	10	8
(b) Right Ventricle, Selective	32	25
(c) Right Atrium, Selective	10	8
(d) Intravenous	2	2
V. *Femoral Arteriography*	38	25
VI. *Venography*		
(a) Axillary	20	5
(b) Femoral	29	22
(c) Inferior Vena Cavagraphy	2	2
(d) Intercostal and Interspinous	7	4
(e) Splenoportography	2	2
Total Examinations		1,035
Total Injections	2,504	

new procedure devised by one of us.[4] A Seldinger catheter is placed in the aortic arch by the percutaneous transfemoral method. Injection of the arch or a selective injection of the innominate artery or left common carotid artery is performed. The patient is placed in the supine position and the chin is hyperextended and a single roentgenogram is made using a wedge filter to compensate for the lesser exposure needed for the chest and aortic arch. Excellent filling of the vessels of the aortic arch and the cerebral vessels is obtained. After performing this procedure, the cathe-

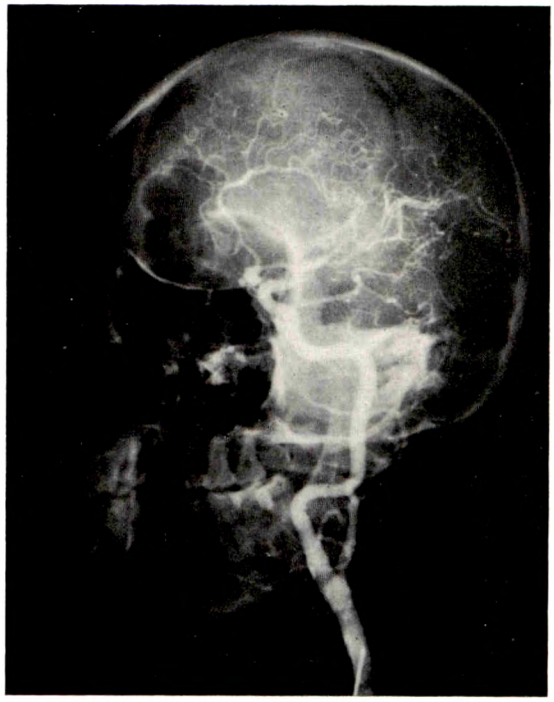


FIG. 2. Cerebral angiogram with 8 cc. of 60 per cent meglumine iothalamate 1 second after the start of injection demonstrating an aneurysm of the anterior communicating artery.

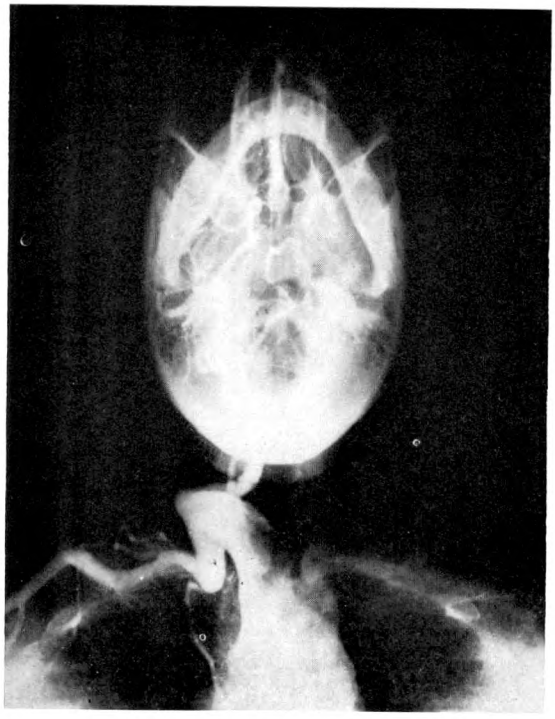


Fig. 3. Demonstration of an innominate artery aneurysm with 45 cc. of 80 per cent sodium iothalamate in a 57 year old Negro female. Selective placement of the catheter in the innominate artery by the percutaneous femoral method.

ter is pulled down and a renal arteriogram is obtained. We have performed this examination, using Angio-Conray, on 18 patients without any serious complications (Fig. 3, 4 and 5). Several patients received over 150 cc. when multiple injections were performed without any side effects. In one patient with a large innominate artery aneurysm, we selectively placed the catheter within the innominate artery, the left common carotid artery and the aortic arch. Forty-five cubic centimeters of Angio-Conray were injected using 5 kg./cm.^{2} pressure at each site. The patient experienced no demonstrable side effects.

Percutaneous femoral catheterization using the Seldinger technique for renal arteriography has been performed on 35 patients with a total of 45 injections. Rapid film exposures were made with the Elema unit, and a Gidlund pressure injector was used for the injection. Thirty to thirty-five cubic centimeters of Angio-Conray were used with 5 kg./cm.^{2} pressure for each injection.

Two patients experienced some back pain when a 1 mm. catheter with 6 kg./cm.^{2} pressure was used. When the pressure was 5 kg./cm.^{2}, none of the patients experienced back pain. When we used the 3 mm. lumen Seldinger catheter, much better filling of the renal vessels was obtained. The evidence of side effects was less than with the other common opaque media. The very low viscosity of Angio-Conray with a high iodine content and a low toxicity is felt to approach the ideal medium for renal angiography (Fig. 6).

Multiple renal arteries on each side were found in 30 per cent of our patients. One patient had three renal arteries arising from the aorta and one from the internal iliac artery supplying the right kidney and two renal arteries supplying the left kidney (Fig. 7, *A* and *B*).

Angiocardiography was performed on 41 patients. This series included septal defects,

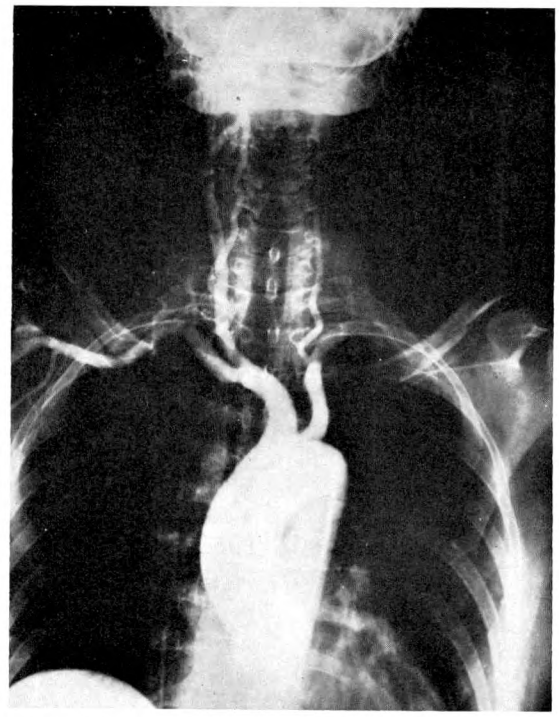


Fig. 4. Aortocaroticocerebral angiogram with 45 cc of 80 per cent sodium iothalamate showing complete occlusion of the left common carotid artery at the point of origin.

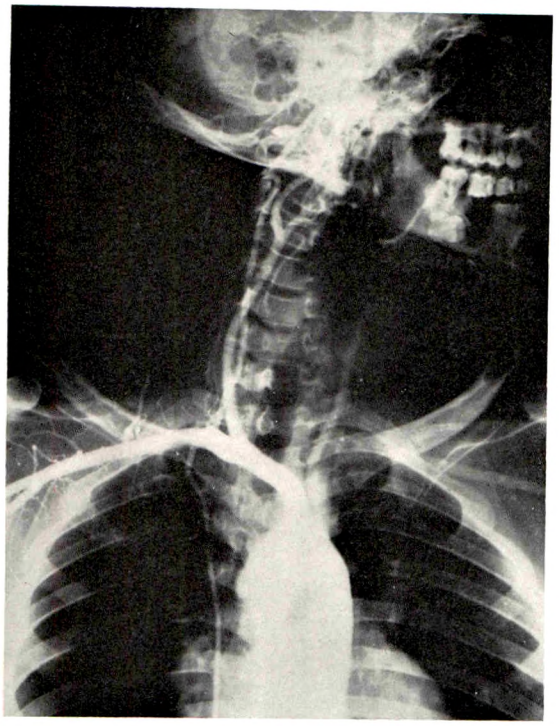


Fig. 5. Aortocaroticocerebral angiogram with 45 cc. of 80 per cent sodium iothalamate demonstrating a normal innominate artery and a right vertebral artery.

patent ductus and cyanotic congenital heart disease. The incidence of side effects was felt to be less than with other opaque media. Several adult patients received 80 cc. of Angio-Conray injected directly into the right ventricle through a catheter without any side effects.

Cineangiography with a catheter in the right ventricle was performed on 25 patients. Conray is adequate in children and it was felt to give a greater density than sodium diatrizoate 50 per cent. The dosage of the Angio-Conray was calculated on the basis of the body weight, *i.e.*, 1.3 cc./kg. or less for angiocardiography, 0.5–0.88 cc./kg. for aortography.

Conray is felt to be adequate for femoral arteriography. We have performed 25 femoral arteriographies with a total of 38 injections without any complications (Fig. 8).

Intravenous angiography has been performed on 35 patients with a total of 60 injections. One patient had four axillary venographies with the arm up and the arm down position, plus two cinevenographies using Angio-Conray in a 2 month period (Fig. 9). A total of 600 cc. was given without any side effects. During the last axillary venography, 20 cc. of Angio-Conray was injected subcutaneously into the arm. It was felt that this caused less pain and redness than had occurred with other opaque materials.

Several intraosseous venographies have been performed and none of the patients experienced any side effects. Figure 10 demonstrates complete superior vena cava obstruction in a 39 year old white male who was given 25 cc. of 80 per cent sodium iothalamate. A catheter was placed in the left innominate vein by the percutaneous femoral method. The film was exposed 0.8 seconds after the beginning of the injection using a Gidlund pressure injector with 5 kg./cm.^{2} pressure. The patient experienced no side effects.

Injections were performed on 20 patients without any difficulty in cystographies,

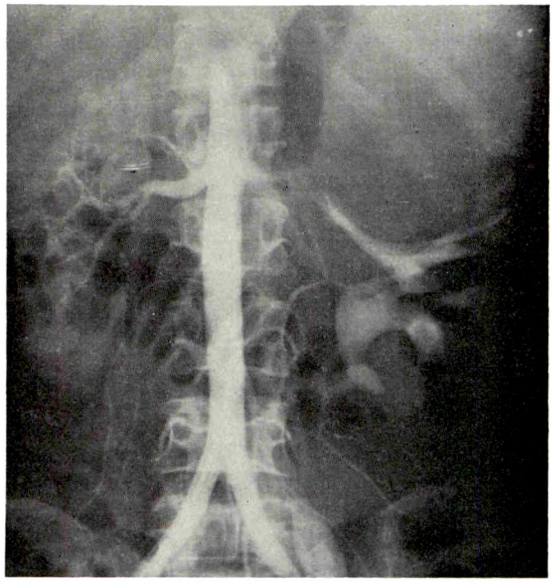


Fig. 6. Abdominal aortogram-renal arteriogram with 80 per cent sodium iothalamate. Injection of 30 cc. following percutaneous femoral catheterization using 5 kg./cm.^{2} in a 32 year old white female. Twenty cubic centimeters of 60 per cent meglumine iothalamate were injected intravenously prior to the aortography. A large hypernephroma of the upper pole of the left kidney is demonstrated.

upper gastrointestinal studies and in examinations for fistulas.

DISCUSSION

Conray and Angio-Conray are felt to be superior to all known radiopaque materials. Conray is the preferred agent for intravenous urography, cerebral angiography, femoral arteriography and venography. Angio-Conray is the agent of choice for aortography and angiocardiography.

Several experimental tests showed Conray and Angio-Conray to be less toxic than any of the available contrast media. It is felt that a solution with 28 per cent iodine is a good "all purpose" contrast agent. The 48 per cent iodine content of Angio-Conray is higher than that of any opaque on the market. For years a solution with a higher

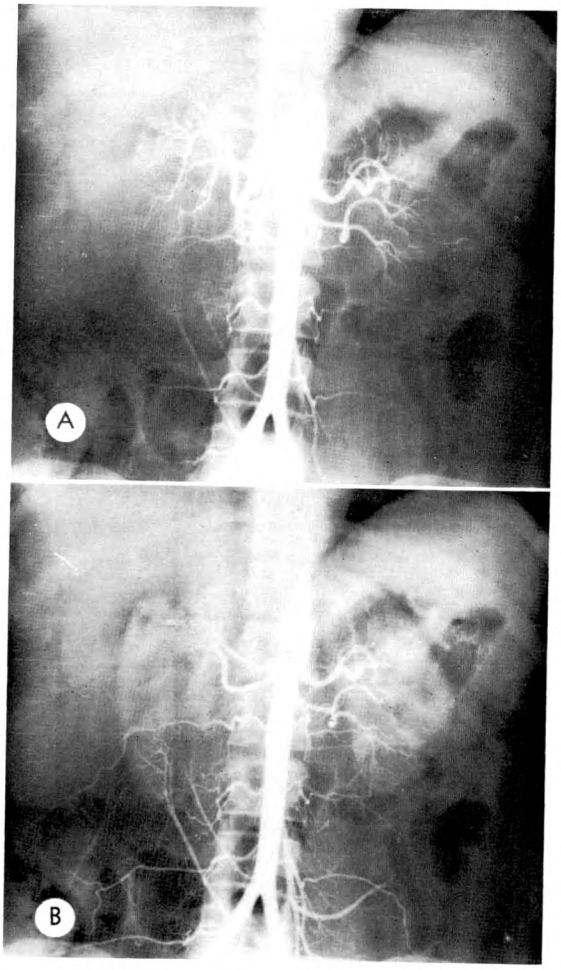


FIG. 7. Abdominal aortogram-renal arteriogram with 80 per cent sodium iothalamate. Injection of 30 cc. with 5 kg./cm.^{2} pressure following percutaneous femoral catheterization in a 35 year old white female. (*A*) Multiple renal arteries with one renal artery arising from the right internal iliac artery. (*B*) Exposure 0.8 seconds after *A* showing better filling of the lower right renal arteries.

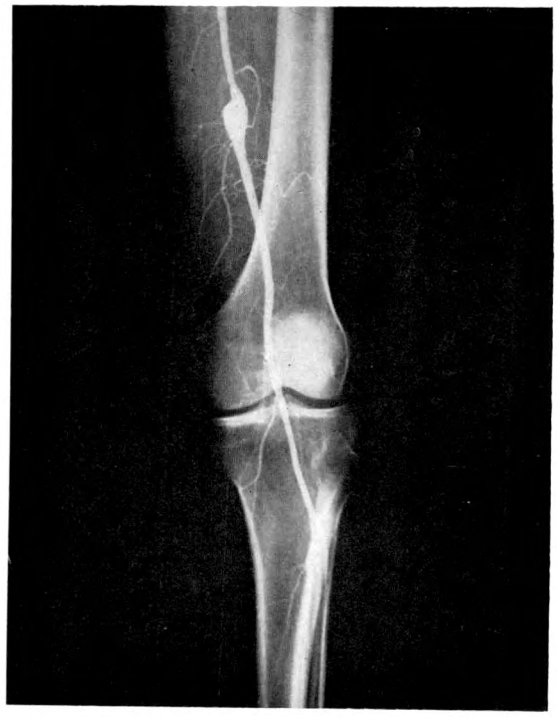


FIG. 8. Femoral arteriogram with 20 cc. of 80 per cent sodium iothalamate showing patency of the postoperative graft of the superficial femoral artery.



FIG. 9. Postoperative axillary venogram with 30 cc. of 80 per cent sodium iothalamate showing patency of the venous graft.

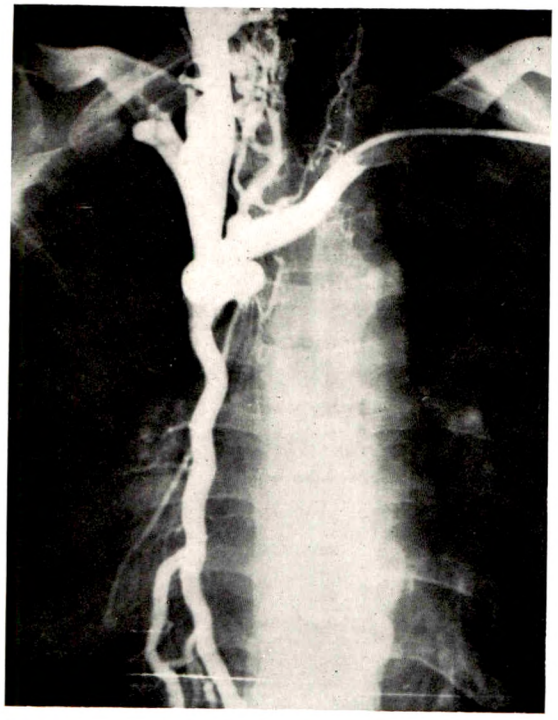


Fig. 10. Demonstration of superior vena cava obstruction in a 39 year old white male with 25 cc. of 80 per cent sodium iothalamate.

iodine content and lower viscosity was needed for angiography and angiocardiography. The lack of stickiness of Conray and the only very slight stickiness of Angio-Conray is of definite advantage during injection. This is one characteristic that was appreciated by all using the compound. The lower viscosity makes possible the use of less pressure, and a small catheter can be employed for selective arteriography which will result in a much better bolus than when the higher viscosity opaque materials are used.

Conray and Angio-Conray are clear colorless solutions at room temperature and require no warming.

CONCLUSIONS

Meglumine iothalamate 60 per cent (Conray) produces considerable density and excellent contrast and has low viscosity. It has a low degree of pharmacologic toxicity and a high degree of patient safety. It is rapidly excreted by the kidneys. It is an excellent medium for intravenous urography, cerebral angiography and femoral arteriography. It is not sticky and does not cause "locking of the barrel of the syringe."

Sodium iothalamate 80 per cent (Angio-Conray) provides a solution containing more iodine (48 per cent) than any other contrast medium. It has a low viscosity and because of its high solubility it is a completely dissolved clear solution even below room temperature. It is very similar in viscosity and iodine content to urokon 70 per cent and has a lower toxicity than any similar opaque medium. Satisfactory visualization can be obtained with injections of 0.2–0.3 cc./pound body weight. It is an excellent medium to be injected through catheters under pressure. It is the medium of choice for angiocardiography and angiography.

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ADDENDUM

Since this paper was accepted for publication, we have used Conray 60 per cent and Angio-Conray 80 per cent in a new procedure of direct percutaneous non-catheter left and right brachial angiography. Angio-Conray 80 per cent produces excellent visualization of the thoracic and abdominal aorta when injected by the left brachial (pan-arteriography) method. Conray 60 per cent has been employed for the right brachial cerebral angiography studies.

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X-RAY EXAMINATION WITH AN IMPROVED X-RAY TELEVISION UNIT

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OSAKA, JAPAN

IN OUR previous paper,[2] we reported the construction and diagnostic application of an x-ray television unit with a vidicon-image intensifier combination system which was first introduced for practical use in Japan. The unit then reported, for all its diagnostic advantages, had several disadvantages. These were as follows:

1. The tilting table for the x-ray television unit was not operated by remote control; hence, operators and physicians were not completely protected from radiation exposure.

2. The image intensifier that was combined with a vidicon camera had only a 5 inch diameter which proved rather unpopular in diagnostic practice in terms of area and speed.

3. The television broadcasting standard with 525 scanning lines showed a rather poor efficiency in transmitting x-ray television signals.

4. An ideal x-ray television unit for roentgen diagnosis should be capable of telefluoroscopy, telefluororoentgenography, telecineroentgenography and remote control direct roentgenography used singly or in combination.

In the present communication the efforts which were made to improve the original x-ray television unit are being reported.

REMOTE CONTROL FLUOROSCOPIC TABLE FOR X-RAY TELEVISION EXAMINATION

In order to utilize the x-ray television system so that images could be observed in a separate radiation-free room, we devised a diagnostic table with full remote control operation (Fig. 1).

Possible Movements of the Fluoroscopic Table. The table is capable of three different types of movements, longitudinal sliding, lateral traverse and up-and-down tilting (Table 1). Since this range of movements offers complete roentgenographic coverage of the desired area, satisfactory gastrointestinal examinations, chest and heart surveys, studies of bones and joints, pyelography, bronchography, cholecystography, myelography and angiocardiography can be carried out.

Focus-Screen Distance. The x-ray tube focus-screen distance is changeable within limits of 80–130 cm. by remote control. The distance of 80–100 cm. is employed for telefluoroscopy, and the longer one for direct spot roentgenography so that undesired enlarged images are eliminated. This procedure is especially useful for examinations of the chest, including bronchography, examinations of bones and joints and for pyelography. The distance between focus and screen is indicated on the remote control panel by a digit system.

Shutter. The conventional shutter allows only a right angle quadrilateral field. The present unit is equipped with an image intensifier for a round visual field. Thus, if this intensifier is employed with the conventional shutter, unfavorable situations are very likely to arise.[3] The use of an image intensifier in its full size would produce exposure of an unnecessary portion of the patient's body. An attempt to eliminate such superfluous exposure would result in a rather limited quadrangular visual field inscribing a circle (Fig. 2). This is apt to cause not only an overexposure of the pa-

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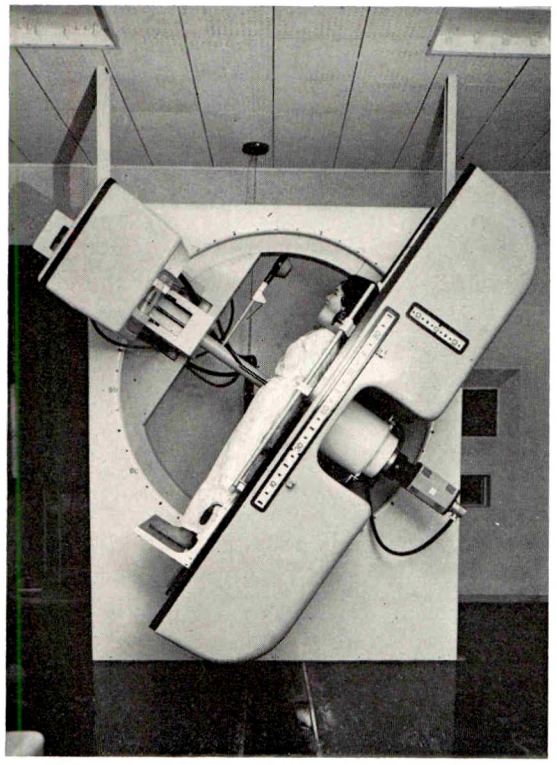


Fig. 1. The diagnostic table which is used with the x-ray television unit for roentgen diagnosis is operated completely by remote control.

tient but also a low viewing efficiency in television due to increase in scattered rays.

Because of these reasons, we designed a new type of shutter for telefluoroscopy, with which we can obtain three shapes of the visual field; (a) a circle 9 inches in diameter, (b) an elongated area with a width of 5 inches (2.5 inches to each side of midline), and (c) a 5×6 inch rectangle. In practice, (a) is used for the chest, heart, gastrointestinal tract and skull examinations as well as for pyelography and bronchography; (b) for examinations of the esophagus, long bones and vertebral column as well as for myelography; and (c) for examinations of the pyloric antrum, duodenal bulb, joints of the extremities and for cholecystography.

During operation, even if the distance

Table I

Movements of the Remote Control Fluororoentgenographic Table

Types of Movements	Range	Speed
Longitudinal Sliding	±50 cm.	3.5 cm./sec.
Lateral Traverse	±12.5 cm.	3.0 cm./sec.
Up-and-Down Tilting	±90°	90°/20 sec.
		90°/40 sec.

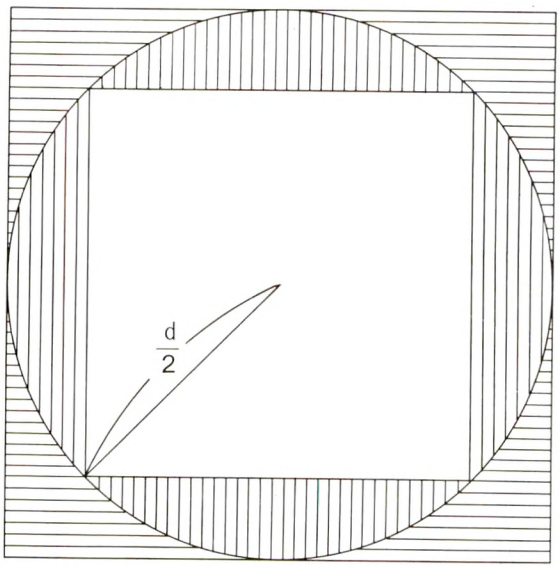


Fig. 2. Diagram showing the area which receives superfluous irradiation (horizontal lines) and the loss of the effective visual field (vertical lines) when the combination of the usual multi-leaf shutter and an image intensifier is used.

In the former, suppose the diameter of the input screen of an image intensifier is d, the ratio of the superfluous field to the entire visual field of an image intensifier is as follows:

$$\frac{d^2 - \frac{\pi d^2}{4}}{\frac{\pi d^2}{4}} \times 100 = \frac{4-\pi}{\pi} \times 100 = 27\%.$$

In the latter, the ratio of the loss of the effective visual field to the entire visual field of an image intensifier is as follows:

$$\frac{\frac{\pi d^2}{4} - \frac{d^2}{2}}{\frac{\pi d^2}{4}} = \frac{\pi - 2}{\pi} \times 100 = 36\%.$$

between the x-ray tube focus and the screen is changed, an automatic control keeps the size of the fluoroscopic field constant. Whenever telefluoroscopy is followed by direct spot roentgenography, the shutter is automatically adjusted for a full-size film. Regardless of the size of film employed, the roentgenographic field is always kept constant, irrespective of a focus-screen distance.

Remote Control Direct Roentgenography. Diagnostic procedures with an x-ray television unit should include not only telefluoroscopy, telefluororoentgenography and telecineroentgenography, but also remote control direct roentgenography, because a full-size film recording is far superior to any other recording method in detail perceptibility. The film size which is used with the present x-ray television system is 14×10, 12×10 and 10×8 inches. As many as 4 full-size roentgenographic films can be held in a magazine on the tilting table as well as a combination of films of different sizes. The size of a film to be used next is indicated on a control panel by a digit system.

Grid. A focussed grid is of a 4.5:1 ratio and 21/cm. density. The grid is fixed in or removed from the visual field by remote control when required, *e.g.*, in chest telefluoroscopy the removal of the grid is advisable to obtain sharpness of image and because of the small dosage desired.

Auxiliary Control Panel in the Examination Room. The operation of the remote control diagnostic table is usually carried out from a radiation-free room which is located away from the examination room. However, in procedures such as catheterization of the cardiovascular system or angiocardiography, physicians and assistants need to remain in the examination room; therefore, a small auxiliary control panel is provided by which to operate the diagnostic table (Fig. 3).

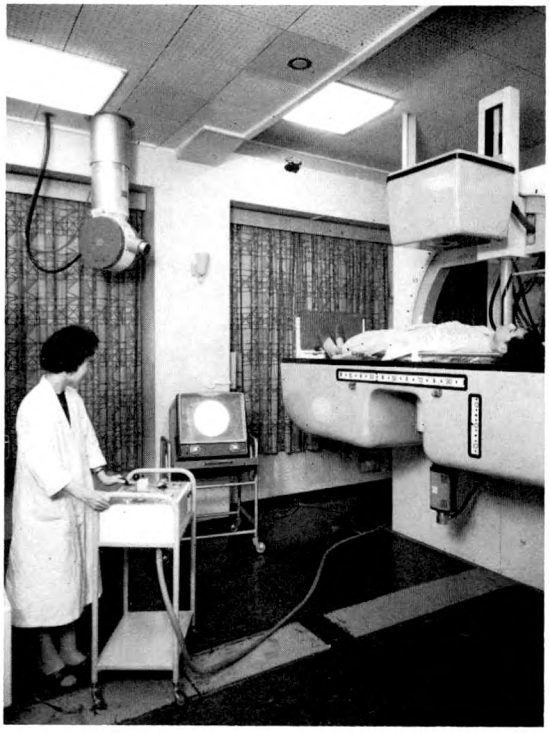


FIG. 3. A photograph showing a diagnostic procedure being carried out in an examination room. A small control panel is provided for the operation of the diagnostic table.

THE X-RAY TELEVISION INSTALLATION

Scanning Standard. In the present x-ray television unit, the images which are enhanced by a 9 inch intensifier are picked up by a high sensitivity vidicon camera; hence, the round viewing screen is always used for the vidicon pick-up. If a round visual field were scanned on the usual right angle quadrilateral field having an aspect ratio of 4:3, an appreciable area of the monitor screen would be left useless in transmitting information, as shown in the shaded portion of Figure 4*A*. We therefore introduced a field with an aspect ratio of 1:1, *i.e.*, the square scanning system. Since the resolving power in a horizontal direction is greater because of the square scanning, we utilized 625 scanning lines instead of 525 to preserve the balance of resolving powers between the vertical and horizontal directions. The scanning standard of the present x-ray television system is shown in Figure 4*B*.

Construction and Function. The x-ray television system can be adjusted for various procedures, *e.g.*, telefluoroscopy for the



Fig. 4. A diagrammatic comparison between the scanning standard of an ordinary system (*A*) and that of a square scanning system (*B*).

Scanning Standard

	(*A*)	(*B*)
Aspect Ratio	4:3	1:1
Number of Scanning Lines	525	625
Frame/sec.	30	30
Interlace	2:1	2:1

chest and heart, and telecineroentgenography for the cardiovascular system and surgical operations. It can be used for mass examinations, especially of the gastrointestinal tract. It can be utilized for telefluoroscopy, 16 mm. telecineroentgenography, 70 mm. telefluororoentgenography and full film-size direct roentgenography. The diagnostic table is operated by remote control and a vidicon camera pickup allows for a general view of the examination room. The general arrangement of the present x-ray television installation is shown in Figure 5. Diagnostic procedures can be carried out in a control room with complete protection from radiation (Fig. 6).

Telefluoroscopy. Telefluoroscopy is usually done with a 14 inch master monitor at the control desk. However, by using a 17 inch auxiliary monitor in the examination room, diagnostic procedures can also be carried out at the side of the tilting table. In addition, 14, 17 or 21 inch television monitors have been placed in each room of the hospital, where discussion of the telefluoroscopic images is desired. The television transmission and private telephone signaling to other rooms are handled at the main television control desk.

Telecineroentgenography. X-ray images are filmed with a 16 mm. cinecamera and projected on a 14 inch monitor screen which has been installed with its surface turned upwards on a side-table of the control desk (Fig. 6 and 7). Since the pictures are transmitted at 30 frames per second, filming speed in telecineroentgenography is controlled with precision at 15 frames per second by means of a synchronous motor. The footage of the used film is indicated at the control desk by a digit system.

Telefluororoentgenography. The unit is so designed that telefluoroscopic images may be kept on record, which is especially useful when mass examinations of the gastrointestinal tract are performed. It also is capable of serial fluororoentgenography, particularly when the use of 70 mm. roll film instead of 16 mm. cinefilm is desired. A 70 mm. automatic serial roentgenographic camera is installed on the side table of the control desk (Fig. 7). There are two methods of filming: digital spot roentgenography and automatic serial roentgenography at the rate of 1, 2, 3 or 5 frames per second. Automatic serial roentgenography covers 100 frames at maximum. A monitor screen for telefluororoentgenography was installed on the side table in the same manner as was the monitor for telecineroentgenography.

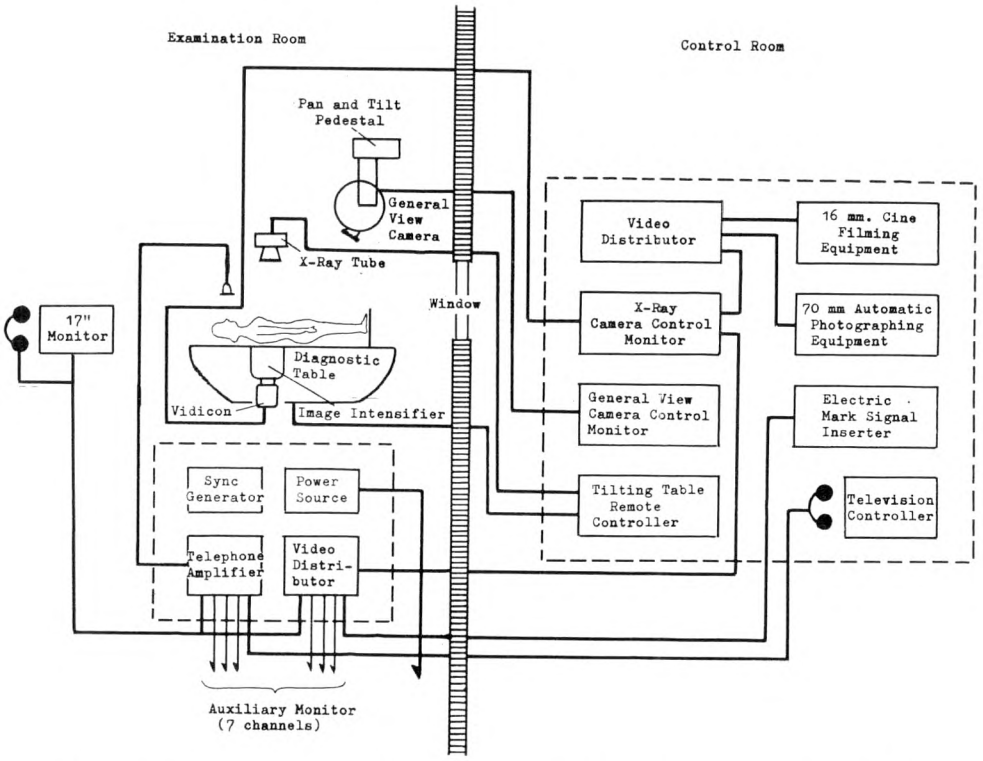


FIG. 5. Schematic drawing of the installation of the present x-ray television unit.

Electric Mark Signal. A triangular mark can be electrically inscribed at any place so that a lesion may be pointed out to observers in other rooms for purposes of discussion or symposia. The mark can be recorded on a 16 mm. cinefilm and/or a 70 mm. spot film.

Monitoring in the Examination Room. A television camera suspended from the ceiling was provided for the purpose of obtaining a general view of the examination room (Fig. 3). Panning, tilting, ascending and descending movements of the vidicon camera are remotely controlled in the con-



FIG. 6. Photograph of the control room of the present x-ray television unit.



FIG. 7. Photograph of a 70 mm. automatic serial roentgenographic camera for telefluororoentgenography and a 16 mm. cinecamera for telecineroentgenography.

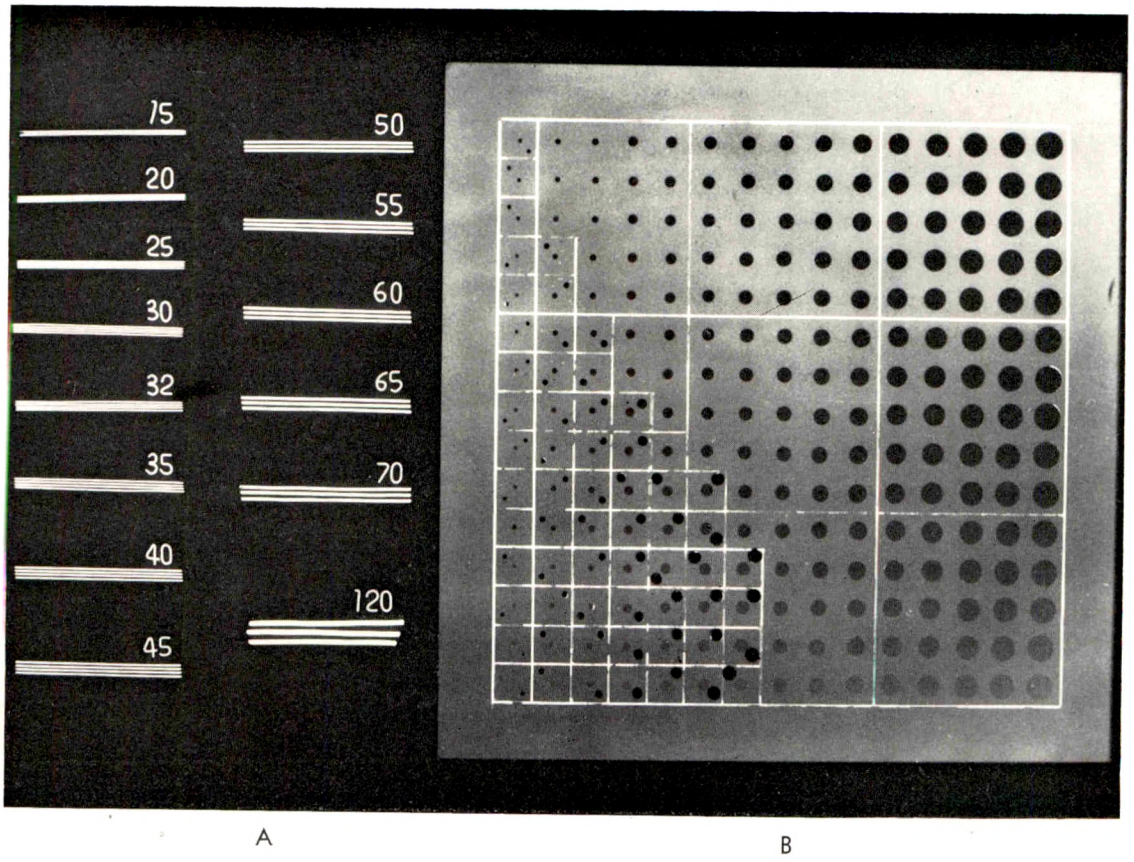


Fig. 8. Copper wire groupings (*A*) and contrast detail phantom (*B*) for testing detail perceptibility.

trol room. Zooming of the televised picture is also possible. A general view of the examination room can be transmitted not only to the control room but to any other room which has been equipped.

DETAIL PERCEPTIBILITY

Measurement of detail perceptibility is accomplished in two different ways, by using: copper wire groupings (Fig. 8*A*) and a contrast detail phantom (Fig. 8*B*). The resolution of the present equipment using copper wires has been studied and compared with that of the previous x-ray television unit (Table II). It was found that the less resolution obtained by using a 9 inch instead of a 5 inch image intensifier was offset by the improved construction of the present television unit. This is not only due to the circuitry and the optical system of the new unit, but also to the adoption of an adequate scanning standard. The employment of a 0.5×0.5 mm. focus size x-ray tube improves x-ray television resolution within a maximum limit of 0.35 mm.

A contrast detail test was performed with a specially prepared phantom (Fig. 8*B*) with interesting results (Table II). Paradoxically, when copper wires are used, the image intensifier is superior to the x-ray television in resolution; however, the former is inferior to the latter when contrast detail is compared. This superiority in low contrast is advantageous in the detection of objects such as stones in a gallbladder or hazy densities in the pulmonary fields. In this respect, Feddema[1] seems to have an opinion similar to ours. He cites an instance of gallstone which was detected by x-ray television in the absence of visualization when an image intensifier was used.

TABLE II

COMPARISON BETWEEN THE DETAIL PERCEPTIBILITY OF THE PRESENT X-RAY TELEVISION SYSTEM AND THAT OF THE PREVIOUS ONE[2]

Method*	Diameter of Discernible Wires (mm.)	Depth (h) and Diameter (d) of Smallest Visible Holes (mm.) d÷h.
Conventional Fluorescent Screen	0.5	4.4
5 Inch Image Intensifier (Philips)	0.25	—
5 Inch Image Intensifier + Vidicon Camera	0.4	—
9 Inch Image Intensifier (Philips)	0.3	2.4
9 Inch Image Intensifier + Vidicon Camera	0.4 (0.35**)	1.8

* Focus-screen distance: 90 cm.
Focus size of the roentgen-ray tube: 1.0×1.0 mm.
** The detail perceptibility when a 0.5×0.5 mm. focus is employed.

TECHNICAL DATA AND DOSE FOR DIAGNOSIS WITH X-RAY TELEVISION

The technical data, patient skin doses and back scatter in telefluoroscopy, telecineroentgenography and gastrointestinal telefluororoentgenography of the present x-ray television unit are shown in terms of kilovoltage-milliamperage in Table III, compared with those of conventional fluoroscopy. It is evident that there is an appreciable decrease in patient dose when the x-ray television system is used. It must be re-emphasized that neither telecineroentgenography nor telefluororoentgenography requires more than the dose received during telefluoroscopy. In diagnostic procedures, the technical data for exposure and patient dose when remote control direct roentgenography is performed with the x-ray television unit are the same as those obtained with full size direct routine roentgenography. This fact permits use with comparative safety to the patient.

TABLE III

PATIENT SKIN DOSE IN TELEFLUOROSCOPY OF GASTROINTESTINAL TRACT COMPARED WITH CONVENTIONAL FLUOROSCOPY

Thickness of Abdomen	Telefluoroscopy			Conventional Fluoroscopy		
cm.	kv.	ma.	Skin Dose (r/min.)	kv.	ma.	Skin Dose (r/min.)
14	52–60	2–2.5	0.54–0.88	72	3	3.20
16	55–68	2–2.5	0.58–1.10	76	3	3.50
18	60–70	2–2.5	0.75–1.24	80	3	3.85
20	62–73	2–2.5	0.87–1.44	84	3	4.40
22	65–75	2–2.5	1.00–1.60	88	3	4.80
24	65–75	2–2.5	1.07–1.70	92	3	5.30
26	65–80	2–2.5	1.10–1.98	96	3	5.50
28	67–82	2–2.5	1.27–2.17	100	3	5.75
30	70–85	2–2.5	1.45–2.48	104	3	6.00
32	80–95	2–2.5	1.94–3.25	108	3	6.26

Focus size of the roentgen-ray tube: 1.0×1.0 mm.
Filter: 1.6 mm. Al.
Grid: {X-ray television—4.5–21/cm. / Conventional fluoroscopy—6.5–24/cm.
Focus-screen distance: 90 cm.
Field size: {X-ray television—23 cm. circle. / Conventional fluoroscopy—23 cm.×23 cm. square.

Table IV

REVISED CLASSIFICATION OF THE ORGANS OR REGIONS OF THE BODY ACCORDING TO THE EASE OF FLUOROSCOPY USING X-RAY TELEVISION

Ease of Fluoroscopy	Organs or Regions (nature of examination)	Direction of Roentgen-Ray Beam
	Esophagus and gastrointestinal tract (oral method)	Anteroposterior, oblique
	Sigmoid colon and large intestine (barium enema)	Anteroposterior, oblique
	Trachea and bronchi (bronchography)	Anteroposterior, oblique and lateral
Extremely Easy	Heart and aorta (plain)	Anteroposterior, oblique
	Spinal canal (myelography)	Anteroposterior, lateral
	Pelvis, calyces, ureter and bladder (intravenous and ascending pyelography)	Anteroposterior
	Lung	Anteroposterior, oblique and lateral
	Bones and joints of extremities	Anteroposterior, oblique and lateral
	Vertebral column	Anteroposterior, lateral
	Hip joint	Anteroposterior
Easy	Gallbladder (cholecystography)	Anteroposterior, oblique
	Splenic and portal veins (percutaneous splenoportography	Anteroposterior
Rather Difficult	Heart and aorta (angiocardiography)	Anteroposterior, oblique

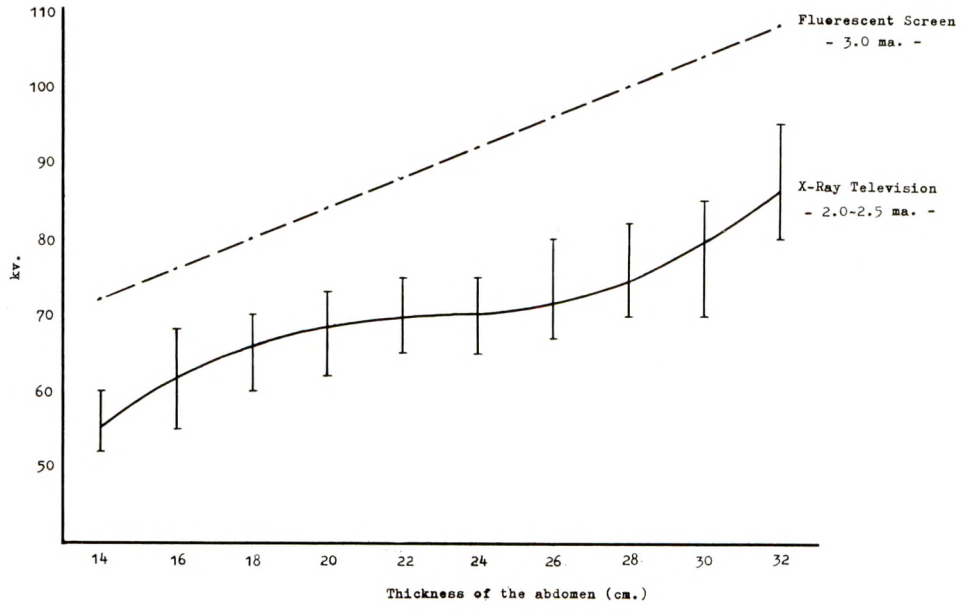


Fig. 9. Technical data in telefluoroscopy of gastrointestinal tract compared with those in conventional fluoroscopy.

DIAGNOSIS WITH X-RAY TELEVISION

The chief advantage of x-ray television diagnosis is that, in examinations where contrast material is used, the organs are easily studied and without radiation exposure to the radiologist. In this regard, a revision has been made in the classification of ease of fluoroscopy which was presented in the authors' previous report[2] (Table IV). The term "difficult" no longer appears since most of the organs or regions have come to be within an "easy" or "extremely easy" x-ray television scope. The thickness of the abdomen no longer interferes with the clearness of the fluoroscopic images of the alimentary tracts, gallbladder, lumbar spine and urinary tract. The examination of the heart and large vessels by angiocardiog-

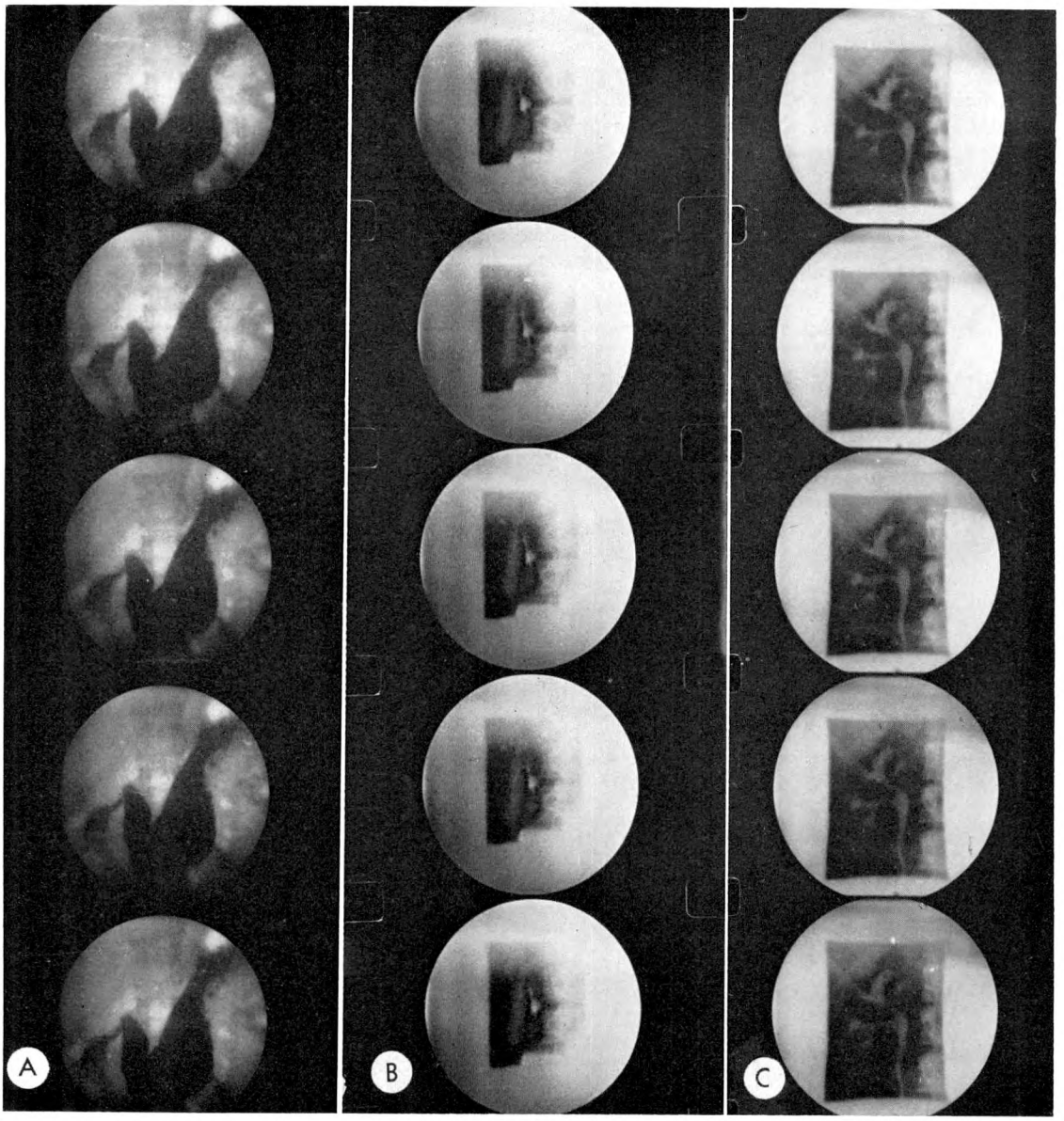


FIG. 10. Telecineroentgenograms showing: (*A*) gastrointestinal tract; (*B*) a gallbladder in cholecystography and (*C*) calyces, pelvis and a ureter in intravenous pyelography.

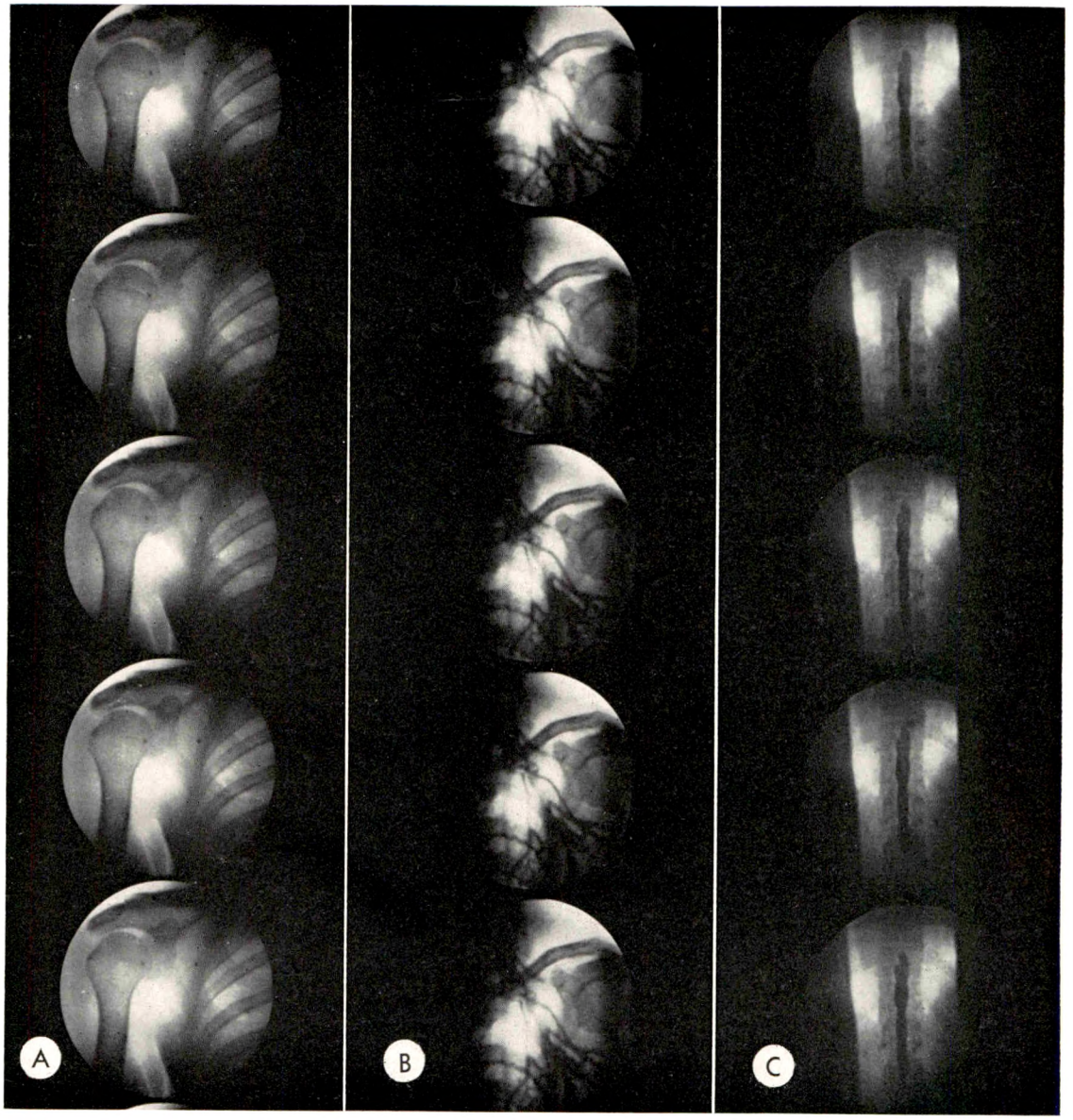


Fig. 11. Telecineroentgenograms showing: (*A*) a shoulder joint; (*B*) collateral veins in venography; and (*C*) a spinal canal in myelography.

raphy is, however, newly classified as being "rather difficult."

The relationship between the thickness of the abdomen and the voltage-milliamperage by which clear telefluoroscopic images of the alimentary tract are obtained is shown in Figure 9 and a comparison is made with conventional fluoroscopy.

Figures 10, *A*, *B* and *C* and 11, *A*, *B* and *C* are telecineroentgenograms and Figure 12, *A* and *B* shows indirect telefluororoentgenograms made by using the 70 mm. automatic serial roentgenographic camera.

Since the beginning of 1961, the authors have employed the present improved x-ray television system instead of conventional roentgenography in all instances of intravenous pyelography, myelography, venog-

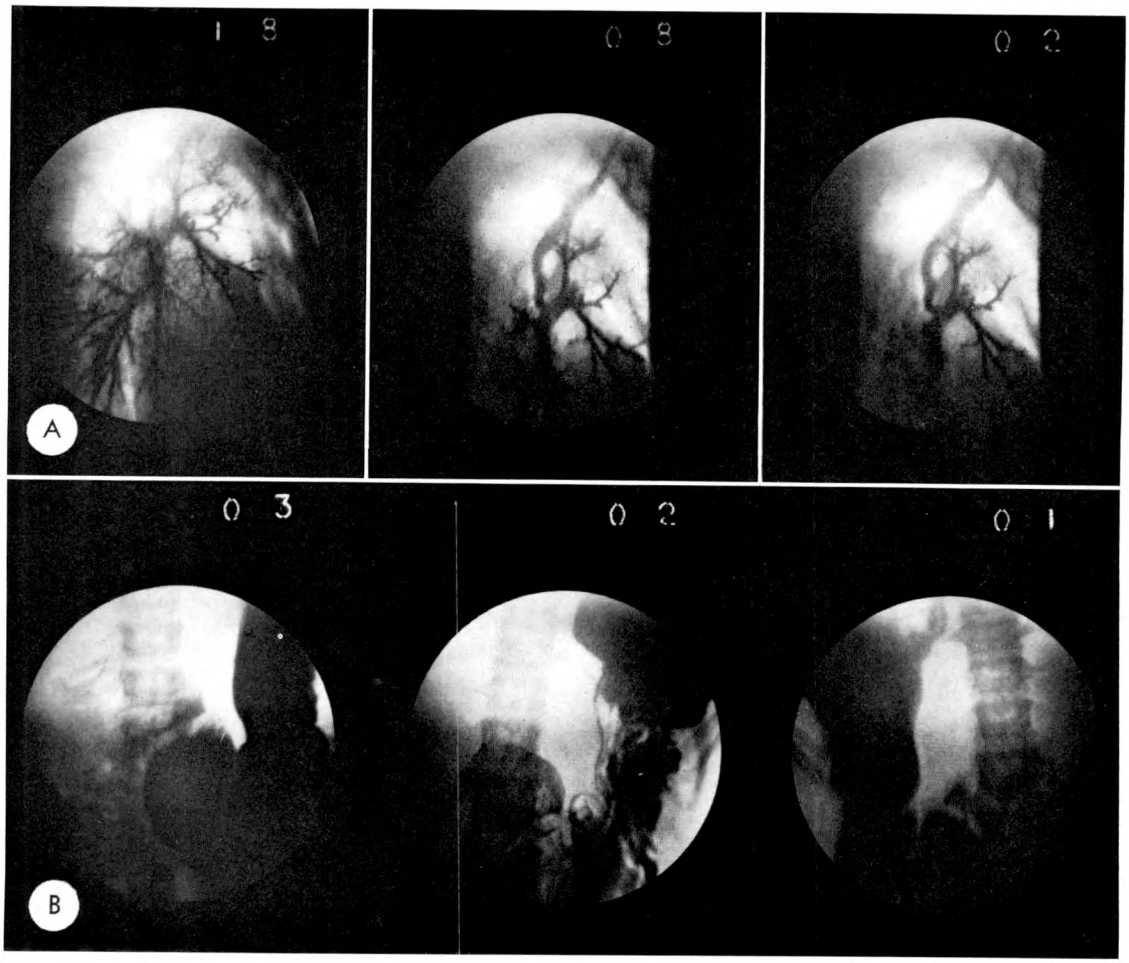


Fig. 12. Telefluororoentgenograms (70×70 mm. size) showing: (*A*) a bronchial arborization in oblique bronchography; and (*B*) a stomach and duodenum, *en face*.

raphy including splenoportography and bronchography and in one-third of the cases requiring gastrointestinal series including cholecystography. It is hoped that with the acquisition of a sufficient number of x-ray television units, all gastrointestinal examinations will be performed in this manner.

SUMMARY

A report is presented of the construction problems, diagnostic application and efficiency of an improved x-ray television system with a remote control fluoroscopic table and a comparison is made with the previously described one. Roentgen diagnosis by means of this unit is discussed.

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Editor: T. Leucutia, 110 Professional Building, Detroit 1, Mich.

Sixty-fourth Annual Meeting: Queen Elizabeth Hotel, Montreal, Quebec, Canada, October 8–11, 1963.

AMERICAN RADIUM SOCIETY

President: Gilbert H. Fletcher, Houston, Tex.; *President-Elect:* Charles G. Stetson, Englewood, N. J.; *1st Vice-President:* Jean Bouchard, Montreal, Can.; *2nd Vice-President:* Lemuel Bowden, New York, N. Y.; *Secretary:* Justin J. Stein, Los Angeles, Calif.; *Treasurer:* Joseph H. Farrow, 112 East 74th Street, New York 21, N. Y.

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Representatives on the National Committee on Radiation Protection: Robert Robbins, Philadelphia, Pa.; Herbert M. Parker, Richland, Wash.

Representative on the Board of Chancellors of the American College of Radiology: Milford D. Schulz, Boston, Mass.

Forty-fifth Annual Meeting: Mark Hopkins Hotel, San Francisco, Calif., April 1–4, 1963.

EDITORIAL

DYNAMIC CONTINUOUS ROENTGEN FLUORODENSITOMETRY

THE combination of physiologic and roentgen techniques has produced numerous procedures useful in diagnosis of cardiovascular diseases. Dynamic evaluation of cardiopulmonary densities as a measure of displaced volume or mass remains a difficult problem of mutual concern. Although judicious application of image intensification has decreased hazardous radiation exposure during fluoroscopy and cineroentgenography, the primary detection of quantitative segmental deviations in volume or density evades reasonable numerical expression to date.

The recent good correlation[1] shown between electrokymograms and segmental radiofrequency electrical impedance plethysmograms merits further investigation. We definitely tend to ignore the degree of dynamic roentgen fluorodensity, or manifest pulsation of peripheral or hilar lung region and cardiac chambers. Both of the above procedures easily identify significant variations in patterns of pulmonic, great vessel and cardiac volume pulsations and are capable of quantitative assessments.

Quantitative volume deviations by impedance studies[1] are calculated from the parallel resistive impedance component produced by the segmental blood volume variations in a given body conductor. Parallel resistances are substituted as volume standards in peripheral vascular studies. This implies knowledge of the over-all segmental resistance, the blood resistance and the incremental quantitative change in series electrical resistance. The stroke volume is more difficult to define in terms of "electrical volume," due to the complexity of the thorax as an electrical conductor. With respect to roentgen fluorodensity variations, it is necessary to account for over-all density as well as incremental series change before quantitative recovery of volume changes can be formulated by roentgen techniques in absolute physical terms. Ring and his collaborators[2] introduced a pressdwood calibrator with each alternate beat in the Chamberlain electrokymographic records. It seems possible and expedient to fabricate standard density equivalents referable to a given depth and cross section of blood for a given field. This would enhance the value of subjective estimations of segmental roentgen density as described for instance by the Capetown Research group.[3] Recently, Oderr *et al.*[4] extended the use of dynamic roentgen fluorodensity techniques to segmental respiratory changes as well as to cardiovascular pulsations. Uniform calibration of densities is adjusted in their study so that the base lines from which breathing patterns are recorded are equivalent in two or more lung segments.

Such an approach would seem to indicate that it is quite feasible to determine stroke volume and cardiac output dynamically by continuous fluorodensography and to quantify the pulsatile lung densities in terms of the central cardiac change which is in the order of one thousandth of the

[1] NYBOER, J. Electrical Impedance Plethysmography; The Electrical Resistive Measure of the Blood Pulse Volume, Peripheral and Central Blood Flow. Charles C Thomas, Publisher, Springfield, Ill., 1959.

[2] RING, G. C., OPPENHEIMER, M. J., LEE, A. J., and CLIREHUGH, J. Automatic calibration of electrokymograph cardiac densograms. *J. App. Physiol.*, 1953, *5*, 513–514.

[3] FOUCHÉ, R. F., BECK, W., and SCHRIRE, V. Roentgenologic assessment of degree of left-to-right shunt in secundum type atrial septal defect. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1963, *89*, 254-278.

[4] ODERR, C. Fluorodensitometry; regional ventilation in lung. Exhibit at 15th Annual Conference on Engineering in Medicine and Biology, Chicago, November, 1962.

body mass. Recently, work by Allison *et al.*[5] shows that a high degree of correlation exists between chest electrical impedance changes and direct spirometric volumes. Segmental spirometry is difficult to apply; however, it is speculated that segmental chest impedance plethysmograms closely parallel regional chest fluorodensograms and segmental pulmonary blood flow. The segmental fluorodensographic techniques together with simultaneous polygraphic correlates of electrocardiograms, phonocardiograms and other cardiovibratory information should elucidate the currently inadequate qualitative descriptions of pulsatile hemic and pulmonary densities. These phenomena, if coordinated on magnetic tapes or equivalent recorders with segmental cineroentgenography for exact localization of the study, should lend themselves to immediate or delayed retrieval for display and automatic computations of meaningful dynamic cardiopulmonary densities.

Soon after 1947,[6] when this JOURNAL editorially commented on the roentgen kymography and roentgen electrokymography,[7] there has been an unexpected decrease in the use of these methods although their value has often been confirmed clinically. On the other hand for more than a decade the techniques of catheter probing for local pressures, flow, sound, angiocontrast and oxygen tension data have continued unabated under the fluoroscope. Under image intensifications, cardiofluoroscopic procedures are now markedly prolonged while the electrocardiographic monitors warn of imminent dangers to rhythm and conduction of the heart.

Further basic work is sorely needed for continuous and discontinuous roentgen fluorodensitometry on its own merit as an index for quantifying mass of blood, fluid or tissues. Unlike roentgen-ray and radiofrequency energies, echo-sonar signals do not penetrate air containing tissues; therefore, they are not very adaptable extrinsically to the chest. Existing correlation of divergent pulse forms with disease entities requires further confirmation and expansion. This type of data when defining obstruction, insufficiency, enlargement or shrinkage is often adequate to diagnose or support the history and clinical findings and could well serve in better management of therapies if quantifiable graphically or numerically. The advantages of a differential diagnostic method such as roentgen fluorodensitometry without anesthesia, without cut-down, without blood letting and without danger of added infection should justify further pursuit of this old but promising technique. In many respects this type of storable dynamic information parallels that of cardiac catheterization which is often resorted to with inconclusive results.

In theory, both roentgen fluorodensitometry and electrical impedance plethysmography[8] give information on physical measures of displacement or on derivatives of displacement and flow, which is as direct as that obtained by the Fick and Stewart dilution time technique. As per Poiseuille's law, pressure *per se* will not measure flow for lack of dynamic hindrance data. On the other hand, the ratio of pressure to hindrance is a measure of volume per unit time. This detection of changing volume by impedance or changing mass per unit volume by densitometry constitutes important indicators of displacement and responses to flow following fluid or gas pressure gradients across unknown dynamic hindrances. By this concept, the so-called roentgen fluorodensograms are basic information from which segmental and gross flow may potentially be determined.

[5] ALLISON, R. D., HOLMES, E. L., and NYBOER, J. Electrical resistance changes occurring in thorax of normal man during respiratory activity. Proceedings of the Am. Physiol. Soc., Vol. 2c, 1962.

[6] LEUCUTIA, T. Roentgen kymography and roentgen electrokymography. AM. J. ROENTGENOL. & RAD. THERAPY, 1947, *57*, 629–631.

[7] CHAMBERLAIN, W. E. Roentgen electrokymography. *Acta radiol.*, 1947, *28*, 847–858.

[8] NYBOER, J. Highlights in electrical impedance plethysmography or pulse volume and flow indices derived from segmental electrical impedance characteristics. In Data Acquisition and Processing in Biology and Medicine. Kurt Enslein. Pergamon Press, 1962, pp. 133–145.

Elsewhere,[8] we have proposed the early end-systolic gradient of peripheral pulses as nature's computed expression of segmental flow run-off of an arteriovenous volume-pulse, recorded mechanically or by electrical impedance methods. This same information and analysis is applicable to peripheral fluorodensograms or pulsations and may easily be confirmed by study of pulsatile flow models. Facilitation of flow information may be derived by extrapolation and differentiation of the arteriovenous volume pulse then computed or compared to equivalent simulated electrical slopes representing regional volume/time or regional density/time relations. Such a method has been proposed in our laboratory.

As all diagnostic methods are man-designed and human engineered, they are subject to false positive, false negative and equivocal results. Further experience usually narrows the margins of error in any technique. We as physicians, other scientists and instrument manufacturers should aim at reducing morbidity and mortality risks which could be avoidable. Concerted or individual effort might well forestall such costly and time consuming procedures by better documenting the fluoroscopy on tape and with computer aids for equivalent or better analysis of the dynamic roentgen-ray field.

In conclusion, a challenging and never aging quotation pertinent to the science of roentgen fluorodensitometry was well penned by Lord Kelvin, who stated, "I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of Science, whatever the matter may be."

Jan Nyboer, D.Sc., M.D.

Cardiovascular Physiology Laboratory
Harper Hospital
Detroit 1, Michigan

NEWS ITEMS

FIFTIETH ANNIVERSARY OF THE NEW YORK ROENTGEN SOCIETY

On November 19, 1962, the New York Roentgen Society, one of the oldest radiological organizations in the United States, celebrated the fiftieth anniversary of its existence at the New York Academy of Medicine. Among its founders was Dr. Eugene Caldwell, in whose memory the Caldwell Lecture of the American Roentgen Ray Society was established in 1920.

The principal speakers on this occasion were Dr. Ross Golden, Emeritus Professor of Radiology, Columbia University, New York, and Dr. Philip R. Allison, Nuffield Professor of Surgery, Oxford University, England. More than 25 past presidents of the Society also took part in the program.

Dr. Golden, whose Columbia career extended nearly a third of a century, discussed the *Essence of the Art of Medicine.* In this masterful essay he stated that "Wisdom is the exercising of sound judgement or discernment, and the ability to perceive and to adopt the best means for accomplishing an end. It is the ability to use and to apply knowledge which cannot be transmitted but is founded on wisdom born of experience and is the essence of training. Herein lies the art as distinguished from the science of medicine."

THE 1963 W. EDWARD CHAMBERLAIN LECTURE

The 1963 Lecture in the Series honoring W. Edward Chamberlain, Emeritus Professor of Radiology, will be given by Robert E. Steiner, Professor of Radiology of the Postgraduate Medical School, London, England, on February 11, 1963 at 4 o'clock P.M. in the Auditorium of the Temple University School of Medicine, 3400 N. Broad Street, Philadelphia, Pennsylvania.

Professor Steiner's subject will be *Radiology of the Pulmonary Circulation.*

COURSE IN RADIOLOGY OF THE GENITOURINARY TRACT

The Department of Radiology of Indiana University School of Medicine announces a postgraduate course in Radiology of the Genitourinary Tract to be given April 17–21, 1963, at the Medical Center in Indianapolis.

The course is planned primarily for the general radiologist but is open to all physicians having an interest in this field. Presentations will consist of lectures, panel discussions, and film interpretation conferences, correlating the radiologic, pathologic, and physiologic aspects of various genitourinary conditions encountered in clinical practice.

Guest participants are well-known teachers in radiology and urology. The faculty includes Drs. J. Scott Dunbar, John A. Evans, Laurence F. Greene, Frank Hinman, Jr., Wyland F. Leadbetter, Harold O. Peterson, Jerome H. Shapiro, and Fred N. Silverman of this country, and Dr. Nils Lindvall of Stockholm, Sweden. The program will also include presentations by the Indiana University faculty.

The subjects for discussion have been arranged so that each day is devoted to one or two major subdivisions of the field, thus facilitating a more comprehensive evaluation of lesions of similar origin, as well as those producing similar roentgen findings.

Further information regarding this course may be obtained by writing the Director of Postgraduate Medical Education, Indiana University School of Medicine, Indianapolis 7, Indiana.

COURSE IN CLINICAL USE OF RADIOACTIVE ISOTOPES

A course in the Clinical Use of Radioactive Isotopes will be given under the supervision of Dr. Sergei Feitelberg and Dr. Edith Quimby of the Department of Radiology, Columbia University, New York City, from June 3 through June 28, 1963. This is a full-time course which includes lectures, experimental laboratory exercises, clinical rounds and clinical measurements on patients and on specimens. In

addition to Drs. Feitelberg and Quimby, the teaching staff will include a number of invited lecturers from the New York area, each presenting material in his own special field.

Enrollment in the class is limited to 20; the fee is $300.

Inquiries should be addressed to Dr. Sergei Feitelberg, Mt. Sinai Hospital, Fifth Avenue at 100th Street, New York, N. Y.

POSTGRADUATE COURSE IN RADIOLOGY AND RADIOACTIVE ISOTOPES

This Annual Postgraduate Course in Radiology and Radioactive Isotopes is presented with the active cooperation of The Radiological Society of Greater Kansas City and generous financial support from The Kansas Division, Inc., of The American Cancer Society, The Kansas State Board of Health, The Kansas Radiological Society and The University of Kansas School of Medicine Radiological Association.

The course lasts 3 days, from February 18–20, 1963, and is devoted to lectures and panel sessions related to roentgen diagnosis, radiotherapy and isotopes. Major responsibility for instruction is carried by a nationally known guest faculty.

For further information please write to: Department of Postgraduate Medical Education, University of Kansas School of Medicine, Kansas City 3, Kansas.

FIFTH INTERNATIONAL COURSE ON TOMOGRAPHY

The Fifth International Course on Tomography will be held at the Istituto di Radiologia dell'Università, Genova, Italy, under the direction of Prof. Alessandro Vallebona.

This course will last 8 days, from September 22 to 29, 1963, and will deal particularly with the recent progress in tomographic methods.

All lectures, while read in the Italian language, will simultaneously be translated into English, French and German.

Those who plan to attend this Course should inform Prof. Renata Vignolini, Secretary General (Istituto di Radiologia dell'Università, Ospedale San Martino, Genova, Italy) who will give details if requested.

FIFTH INTERNATIONAL CONFERENCE ON MEDICAL ELECTRONICS

The Fifth International Conference on Medical Electronics will be held July 22–26, 1963 in the "Centre Européen des Grands Congrès," Esplanade de l'Europe, Liège, Belgium.

The main topic of the conference will be the physical transducer, the transitional device between the living system and its data gathering environment.

The conference languages will be English and French. Provision will be made for simultaneous translation. A scientific and a commercial exhibition will be organized, and one day will be reserved for excursions.

For further information please write to Dr. F. Bostem, Conference Secretary, 23, Boulevard Frère Orban, Liège, Belgium.

AMERICAN CLUB OF THERAPEUTIC RADIOLOGISTS

At its last meeting in Chicago on November 27, 1962, the American Club of Therapeutic Radiologists elected the following officers: President, Dr. Isadore Lampe, Ann Arbor, Michigan, and Vice President, Dr. Franz Buschke, San Francisco, California.

Dr. Howard Latourette of Iowa City was re-elected Treasurer.

DR. EUGENE F. LUTTERBECK HONORED

Dr. Eugene F. Lutterbeck, Radiologist, President of the German Medical Society of Chicago, and immediate Past President of the Jackson Park Branch of the Chicago Medical Society, received the Officers' Cross of the Order of Merit of the Federal Republic of Germany on the occasion of the membership dinner of the German Medical Society at the Germania Club on Wednesday, October 24, 1962.

The award was presented by Dr. Guenther C. Motz, German Consul General of Chicago.

ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

Blood and Lymph System

Bousvaros, G. A., Don, Conway, and Hopps, J. A. An electrical hazard of selective angiocardiography. *Canad. M. A. J.*, Aug. 11, 1962, *87*, 286–288. (From: The Departments of Radiology, Ottawa General Hospital and Ottawa University, and the Medical Electronics Group, National Research Council, Ottawa, Ontario, Canada.)

Wiggers and Wegria demonstrated in dogs that the passage of an electric current through the heart in the vulnerable phase of the cardiac cycle could induce ventricular fibrillation. It has been found that the use of intramyocardial and endocardial electrodes for artificial pace-making in patients with complete heart block has been accompanied by a definite risk of leakage of current through the heart with the production of ventricular fibrillation. The most common way by which this occurs is the leakage of current through the heart from the leads of an inadequately grounded electrocardiograph; the heart is then connected to ground through the intracardiac electrode. If, therefore, in the course of cardiac catheterization or selective angiocardiography, the intracardiac catheter is grounded, the current could flow through the heart from the leads of a "leaking" and ungrounded electrocardiographic amplifier-recorder. Similarly, if the catheter is connected to an electrical potential derived from improperly grounded electrical equipment, current could flow through the catheter to the heart and thence to ground through the leads of an adequately earthed electrocardiographic recorder.

Two instances of ventricular fibrillation are described, one in a 26-year-old man and one in an experimental animal. These episodes occurred during the passage of a catheter into the heart or aortic root under continuous electrocardiographic monitoring. In both instances, the ventricular fibrillation occurred when the intracardiac catheter was connected to an electrically powered injection apparatus. On the strength of subsequent electrical measurements, it is considered that fibrillation in both cases was due to the passage of an electrical current between the catheter tip, acting as an intracardiac electrode, and the limb leads of the electrocardiographic recorder. Passage of the current was attributed to inadequate grounding of the injection apparatus in one instance, and to inadequate grounding of the electrocardiographic recorder in the other.—*William C. McCarty, Jr., M.D.*

Vandendorp, F., Du Bois, R., and Duquesne, R. La phlébographie cave inférieure ou cavographie. (Phlebography of the inferior vena cava or cavography.) *J. de radiol., d'électrol. et de méd. nucléaire*, Mar.–Apr., 1962, *43*, 125–136. (From: Service Central de Radiologie Est, Hôpital Régional, Lille, France.)

Since phlebography of the inferior vena cava was introduced by Reynaldo dos Santos in 1935, numerous techniques have been advanced. These are performed either by direct injection into the vessel or by indirect injection via a tributary or bone. Several osseous avenues have been used, among them the fourth lumbar vertebral body, various parts of the pelvis and the intertrochanteric area.

The authors prefer the technique of Kjellberg, in which 25 ml. of opaque material is introduced high into each femoral vein rapidly and simultaneously, with roentgenograms taken immediately and at 3 second intervals. They feel that a unilateral injection produces nonhomogeneous shadows, and they resort to intraosseous injections only when direct injection into the femoral or long saphenous veins is impossible or further morbidity is feared in the detection of thrombi. On some occasions the authors have found that punctures of the femoral veins were made easier by the application of pressure on a small balloon placed over the umbilicus.

Cavography is contraindicated in severe alterations of hepatic or renal parenchyma, in heart failure, and where there is sensitivity to iodine.—*Frank A. Riebel, M.D.*

Goidanich, I. F., and Campanacci, Mario. Vascular hamartomata and infantile angioectatic osteohyperplasia of the extremities; a study of ninety-four cases. *J. Bone & Joint Surg.*, July, 1962, *44A*, 815–842. (From: Istituto Ortopedico Rizzoli, Clinica Ortopedica della Università di Bologna, Bologna, Italy.)

A classification of vascular hamartomata and vascular dysplasias of the extremities occurring early in life is proposed, based on 94 cases examined by various techniques including arteriography and oxygen saturation studies. Six types were recognized: (1) localized cutaneous and subcutaneous vascular hamartomata; (2) localized deep vascular hamartomata; (3) extensive deep vascular hamartomata; (4) multiple deep vascular hamartomata; (5) diffuse deep vascular hamartomata; and (6) infantile angioectatic osteohyperplasia.

The study indicates that angiomata of the extremities are really hamartomata. The lesions had a propensity for one extremity or one side of the body and in no patient did the lesion grow after the age of 25. Moreover, they were frequently associated with other dysplasias or congenital anomalies. Microscopically, the lesions consist of angioblastic cells and capillaries or cavernous sinuses. The authors propose that vascular hamartomata originate as capillary

vessels which are transformed into cavernous sinuses, pseudoarterioles and pseudoveins.

Arteriovenous fistulae in these lesions are rarely visible on roentgenograms and oxygen content of the venous blood from the affected extremity was elevated in many instances.

The symptoms include pain which may be severe, impairment of muscle and joint function and later deformities due to fibrous contractures. The clinical signs of significance were lengthening of bone and varicose veins. Treatment of the lesions may be successful when they are completely excised, but when they are diffuse or intimately associated with vital structures complete removal is impossible. Amputation may then be necessary.—*F. P. Shea, M.D.*

Guitarte, M. S., Sucari, L., Vilarino, J., Ploszaj, F., and Rubio, H. Cateterismo del sistema venoso suprahepatico. (Catheterization of the suprahepatic venous system.) *Prensa méd.*, Nov., 1961, *48*, 3025–3032.

Catheterization of the hepatic vein can be utilized for study of the dynamics of the portal circulation where splenectomy is being considered for alleviation of repeated esophageal hemorrhage. Under fluoroscopic control, a No. 8 Cournand catheter is introduced into the basilic vein at the elbow and carried to the right auricle. The catheter is then passed into the superior vena cava and into the opening of the hepatic vein. By measurements of the oxygen tension and venous pressure, one can ascertain the percentage of blood flow in the short circulation and find those cases in which a porto-caval anastomosis would be ineffective to relieve portal hypertension.

By means of angiograms, the rate and character of the blood flow in the efferent vessels of the liver can be studied and the presence of communicating vessels not only in the usual areas in the lower end of the esophagus and inferior mesentery veins in the region of the umbilicus but also vessels communicating with the hepatic vein can be identified. The angiograms combined with the clinical examination, laboratory studies, endoscopy and biopsy provide a characteristic picture of Laennec's cirrhosis. Differentiation between intrahepatic tumors and normal liver parenchyma can also be made.—*Murray M. Friedman, M.D.*

Sessions, R. T., Winfrey, E. W., Killen, D. A., and Foster, J. H. Experimental evaluation of a new angiographic contrast medium. *Surg., Gynec. & Obst.*, Aug., 1962, *115*, 187–190. (From: S. R. Light Laboratory for Surgical Research and the Department of Surgery, Vanderbilt University School of Medicine, Nashville, Tenn.)

Toxic reactions to angiographic contrast media have assumed greater importance with development of new techniques and more frequent use of angiography. Previous reports by this group at Vanderbilt University with their studies of toxicity in animals have shown hypaque M 90 per cent least toxic, 70 per cent urokon most toxic.

Conray 80 per cent, a new angiographic contrast medium, 5 acetamido-N-methyl-2,4,6-triiodoisophtalmic acid, was subjected to 2 standardized canine experimental tolerance tests and was found to produce no neuro- or nephrotoxicity. While 6 and 7 cc./kg. of conray 80 per cent produced only 70 and 72 per cent mortality respectively, urokon 70 per cent at 3 cc./kg. or hypaque M 90 per cent at 4 cc./kg. was universally fatal when injected intravenously.

The high iodine content and low viscosity of 1.5 related to water compare favorably to available agents, while the 73 per cent solution shows the most rapid rate of iodine delivery to the vascular system.

The authors conclude that conray 80 per cent is less toxic than any of the currently available contrast media being used for intravenous or intra-arterial studies. Its clinical trial seems warranted.—*Richard E. Kinzer, M.D.*

Gould, R. John, and Schaffer, Burton. The surgical applications of lymphography. *Surg., Gynec. & Obst.*, June, 1962, *114*, 683–690. (From: The Department of Radiology, Philadelphia General Hospital, Philadelphia, Pa.)

This article is presented to illustrate the value of lymphography in the management of various surgical problems. Previous publications from this hospital have described in detail the development of this procedure and the technique utilized. By direct intralymphatic injection of an oily contrast substance, it is possible to evaluate adequately lymphatics of the extremities and of the inguinal, axillary, supraclavicular, external and common iliac, and retroperitoneal areas as well as the thoracic duct.

This procedure has been found to be helpful in the following ways: (1) determining the presence and extent of metastatic malignant lymph node involvement; (2) investigating the mechanisms of production of swollen extremities to differentiate between lymphatic and venous obstruction, or combinations of these; (3) determining completeness of surgical removal of lymph nodes, especially in the axillary, inguinal, pelvic and retroperitoneal areas; (4) evaluating abnormalities of the thoracic duct; (5) determining whether the involvement in lymphomas is localized or generalized; and (6) investigating patients with fever of unknown origin when retroperitoneal lymphoma is a possibility.

Eight representative case histories are discussed, and several reproductions of lymphograms are included. Several new aspects are presently being investigated. Attempts are being made to develop feasible methods of visualizing lymphatics of the

neck, breast, and internal mammary and internal iliac chains. The intralymphatic administration of chemotherapeutic agents and radioactive materials is also being evaluated.—*Douglas S. Kellogg, M.D.*

RADIATION THERAPY

Cook, J. C., and Corbett, D. P. Roentgen therapy of primary gastrointestinal lymphoma. *Radiology*, Apr., 1962, *78*, 562–569. (From: Harper Hospital, Detroit 1, Mich.)

A series of 66 cases of lymphoma which appeared to originate within the gastrointestinal tract or its mesentery is presented. This group constituted 6.5 per cent of the entire series of lymphomas, excluding the leukemias, seen at Harper Hospital (Detroit) from 1922 through mid 1961. Two were considered to be giant follicular lymphoma, 5 Hodgkin's disease, 14 reticulum cell sarcoma and 45 lymphosarcoma. The stage of the disease was classified as to relative localization or generalization at the beginning of treatment. Stage I included involvement of a single lymphatic region or two proximal lymphatic regions, without symptoms of generalized disease. Stage II included detectable clinical involvement of two or more proximal lymphatic regions, with symptoms of generalization, or involvement of two or more distant lymphatic regions. Survival dates were computed from the first roentgen therapy until death or loss to follow-up.

Roentgen therapy was the primary method of treatment in all cases. The majority of patients with Stage I disease were treated by massive technique, with the administration of a tumor dose to superficial lymph nodes of 700 to 800 r at one seance. In treatment of the abdomen, 4 or 5 large portals were used, on successive days for a total tumor dose of 1,200 to 1,600 r in a four to five day period. Lymph node areas adjacent to the known areas of involvement were also treated. The factors used in the treatment of the first cases were 200 kv., 1 mm. Cu filtration and a half value layer of 1 mm. Cu. Somewhat later 225 to 250 kv. constant potential machines with Thoraeus filtration and half value layer of 3 mm. Cu were employed. Recently some patients have been treated with the 2 mev. Van de Graaff type generator with 7.6 mm. Pb filtration and a half value layer of 8 mm. Pb. Tumor doses of approximately 3,000 r have been given in about 4 weeks. In Stage II cases, fractionation was rarely practiced but treatment was given to most lymph node areas. Ten to fourteen large portals were treated in as many days, each node area receiving a tumor dose of 700 to 800 r.

The five year absolute survival for the 42 cases of lymphosarcoma and reticulum cell sarcoma originating in the gastrointestinal tract and mesentery was 35.7 per cent. Of the 9 patients with reticulum cell sarcoma, 4 survived 5 years. Only 2 out of 10 patients with lymphosarcoma of the colon survived 5 years, while 6 of the 11 patients with lymphosarcoma of the stomach were alive at 5 years.

Roentgen irradiation was the primary therapeutic method in all cases and is considered to be the treatment of choice for lymphoma which originates in the gastrointestinal tract or its mesentery.—*A. W. Sommer, M.D.*

Kenyon, Norman M., Soto, Manuel, Viamonte, Manuel, Jr., Parks, Raymond E., and Farrell, John J. Improved techniques and results of lymphography. *Surg., Gynec. & Obst.*, June, 1962, *114*, 677–682. (From: The Departments of Surgery and Radiology, University of Miami School of Medicine, Jackson Memorial Hospital, Miami, Fla.)

Lymphography has proved to be a valuable diagnostic aid and is indicated in the following circumstances: (1) detection and evaluation of lymph node metastasis; (2) differential diagnosis of pelvic masses; (3) evaluation of surgical, chemotherapeutic, and radiation treatment of malignant tumors; (4) determination of the cause of obstructive edema, especially when combined with phlebography; and (5) assistance in the diagnosis and therapeutic control of lymphomas.

The method of visualization of the lymphatics for cannulization and radiopaque media infusion is discussed, and the technique of injection of the opaque medium is described. The authors believe that alphazurine 2G is the most satisfactory dye for initial lymphatic visualization because of its excretion from the body in 36 to 48 hours and its superior staining of the lymphatics. Ethiodol is used for the roentgenographic visualization of the lymphatics because of its specificity for the lymph nodes and its ability to remain in them for from 4 to 6 weeks, permitting repeat studies. The use of green ethiodol now permits visualization of the lymph nodes at operation.

Reproductions of roentgenograms illustrating normal and pathologic findings are included.—*Douglas S. Kellogg, M.D.*

Borsanyi, Steven J. The effects of radiation therapy on the ear: with particular reference to radiation otitis media. *South. M. J.*, July, 1962, *55*, 740–743. (From: The Division of Otolaryngology, University of Maryland School of Medicine, Baltimore, Md.)

Over 100 patients undergoing supervoltage therapy for head and neck cancer were examined at intervals during and after therapy to determine any effects of radiation on the ear. The ears were included in the field in all cases. The patients received between 4,000 and 6,000 r to the region of the inner ear. Fifty to sixty per cent of the patients developed ear symptoms during, or shortly after, completion of therapy.

The most common symptoms were a sensation of fullness in the ear, some loss of hearing, earache and tinnitus.

Examination of the ears revealed a mild to moderate hyperemia of the eardrum with slight retraction in the early stages. There was a moderate conductive hearing loss as well. This disease entity is termed radiation otitis media and the pathophysiologic mechanism is somewhat similar to serous otitis media. Sterile fluid containing some desquamated epithelial cells fills the middle ear. Radiation otitis media usually subsides a few weeks following the completion of radiation therapy.

In the management of the condition, vasoconstrictors, preferably oral, mild analgesics and gentle politzerization were sufficient. In a few cases bacterial invasion resulted in purulent otitis media which required the use of antibiotics. In 10 per cent of the patients necrosis and breakdown of the skin of the external ear canal was noted which was followed by secondary infection. This has been seen less frequently during or following supervoltage therapy than previously with conventional therapy. Functional disturbance indicating cochlea dysfunction was noted. The late effects of radiation on the ear were not studied in detail. The obliterating endarteritis which develops can result in a perceptive type of hearing loss if the blood supply to the cochlea is markedly diminished. Radionecrosis of the auditory ossicles as a late effect is described in the literature. The decreased resistance of the temporal bone against infection is the source of some concern.—*D. Morse, M.D.*

Fischer, H. W., Lawrence, M. S., and Thornbury, J. R. Lymphography of the normal adult male: observations and their relation to the diagnosis of metastatic neoplasm. *Radiology*, Mar., 1962, *78*, 399–406. (From: University Hospital, Iowa City, Iowa.)

Recent roentgenographic study of the lymphatic system has been reported by several authors. Contrast roentgenography of the pelvic and abdominal lymph nodes is stressed in this article. Direct injection of the lymph nodes was tried with both hypaque and ethiodol but abandoned because of leakage. The technique finally selected was visualization of the lymphatics by a blue dye (Patent Blue Violet or Alphazurine 2G is preferred), then cannulation of a lymphatic vessel of the foot with a No. 10 polyethylene tubing, and injection of ethiodol. No undue reactions were noted with 13 injections of lymph trunks.

The normal anatomy was studied in a group of prisoner volunteers, particularly the inguinal, iliac, and aortic-abdominal lymph nodes.

The authors conclude that a constant pattern is not normally to be expected, and that the site of injection makes a difference as to which lymph nodes are visualized. Also, lymph nodes known to be uninvolved by tumor sometimes show radiolucent filling defects. Finally, the lymph nodes visualized by this technique are mainly secondary and not primary lymph nodes in the spread of neoplasms of prostate, bladder, cervix, and uterus.—*J. C. Moore, M.D.*

RADIOISOTOPES

Wagner, Henry N., Jr., McAfee, John G., and Winkelman, James W. Splenic disease diagnosis by radioisotope scanning. *A.M.A. Arch. Int. Med.*, June, 1962, *109*, 673–684. (From: Diagnostic Radioisotope Laboratory, The Johns Hopkins Hospital, Baltimore 5, Md.)

Visualization of an internal organ by radioisotope scanning is primarily dependent on the selective deposition of a γ-emitting radioisotope in the specific organ under study. Successful visualization by this method has been accomplished in thyroid, liver, kidney, brain, and more recently, in spleen. The technique is based on the ability of the spleen to remove damaged red blood cells from the circulation. Red blood cells are labeled with chromium 51, damaged in a manner that results in their sequestration by the spleen, and re-injected into the patient from whom they have been withdrawn. The subsequent scans show the size, shape, position of the organ, and relative function of various portions of the organ.

This report describes the variations in appearance and position of the normal spleen. The method has proven useful in detecting enlargement of the spleen not clinically appreciable, in evaluating the degree of enlargement, in differentiating other abdominal masses from splenomegaly, and in recognizing space-occupying masses of spleen and accessory spleens. Function of spleen could also be estimated, and this application was particularly useful in differentiating sickle cell anemia, which in adults shows a nonfunctioning spleen, from sickle cell variants.

The total dose of radiation delivered to the spleen was calculated to be 6 rad, and the total body irradiation was less than 0.07 rad. No immediate or delayed hematologic or other reactions to the injections of the damaged cells were noted in any of the patients.

Further experience will be required to determine whether the method has usefulness in infectious, cellular proliferative, or lipid metabolic splenomegaly.

The technique has been helpful in studies of the sites and mechanisms of sequestration of damaged and aging red cells, and this is described in a separate previous report.—*Lois Cowan Collins, M.D.*

Adams, Ralph, Hinawi, A. Y., and Qassab, Kh. Localization of hydatid liver cysts with

colloidal radiogold. *J. Nuclear Med.*, July, 1962, *3*, 315–322. (Address: Dr. Ralph Adams, Department of Radiology, Loma Linda University, Los Angeles, Calif.)

The authors report the use of radiogold localization of hydatid liver cysts by "skip" areas where liver tissue is destroyed. Six case histories are presented following discussion of the cycle of Taenia echinococcus granulosis, the causative agent of hydatid cysts.

This procedure should be valuable in areas where hydatid disease is endemic.—*Thomas H. S. Wolever, M.D.*

ROSE, RAYMOND G. Intracavitary radioactive colloidal gold, results in 257 cancer patients. *J. Nuclear Med.*, July, 1962, *3*, 323–331. (From: Endocrine-Isotope Service, Department of Medicine, University of Texas M. D. Anderson Hospital and Tumor Institute, and University of Texas Postgraduate School of Medicine, Houston, Tex.)

The current concepts of the status of intracavitary radioisotope therapy are discussed. Charts and graphs showing the results in 322 instillations of Au^{198} are presented. Of special interest are the groups where this treatment was given with curative intent and as a prevention of ascites.

The results are impressive but still difficult to evaluate.—*Thomas H. S. Wolever, M.D.*

MOLINATTI, G. M., CAMANNI, F., MASSARA, F., OLIVETTI, M., PIZZINI, A., and GIULIANI, G. Implantation of yttrium^{90} in the sella turcica in sixteen cases of acromegaly. *J. Clin. Endocrinol. & Metab.*, June, 1962, *22*, 599–611. (Address: Dr. G. Giuliani, Institute of Pharmacology, University of Milan, Milan, Italy.)

The complications from implantation of yttrium 90 into the sella turcica of 16 acromegalics are discussed.

The aim of treatment is to suppress the hyperactivity of the pituitary gland without destroying it. This was well accomplished, and the complications were minimal.

The laboratory and clinical results were favorable and indicated the efficacy of this form of therapy.—*Thomas H. S. Wolever, M.D.*

MISCELLANEOUS

MASSENTI, S. Su 103 casi di ipertrofia timica roentgenirradiati in età pediatrica e controllati da 6 a 30 anni dopo il trattamento. (On 103 cases of thymus hypertrophy treated by roentgen therapy in pediatric age and controlled from six to thirty years after the treatment.) *Radiol. med.*, Mar., 1962, *48*, 261–279. (Address: Via Roselli, 20, Pisa, Italy.)

One hundred and fifty-two cases were treated over the thymus by roentgen therapy in the Department of Radiotherapy of the Medical School of the University of Pisa between 1930 and 1954. Of these cases, 114 were followed-up but complete information was obtained in only 103.

The patients in infancy were treated because of thymus hypertrophy, while the patients in the adolescent group were treated mainly because of endocrine disorders in which it was thought necessary to inhibit the action of the thymus by irradiation. The latter was the larger group.

The cases were followed-up from a minimum of 6 years to a maximum of 30 years, with an average of 15 years and 7 months.

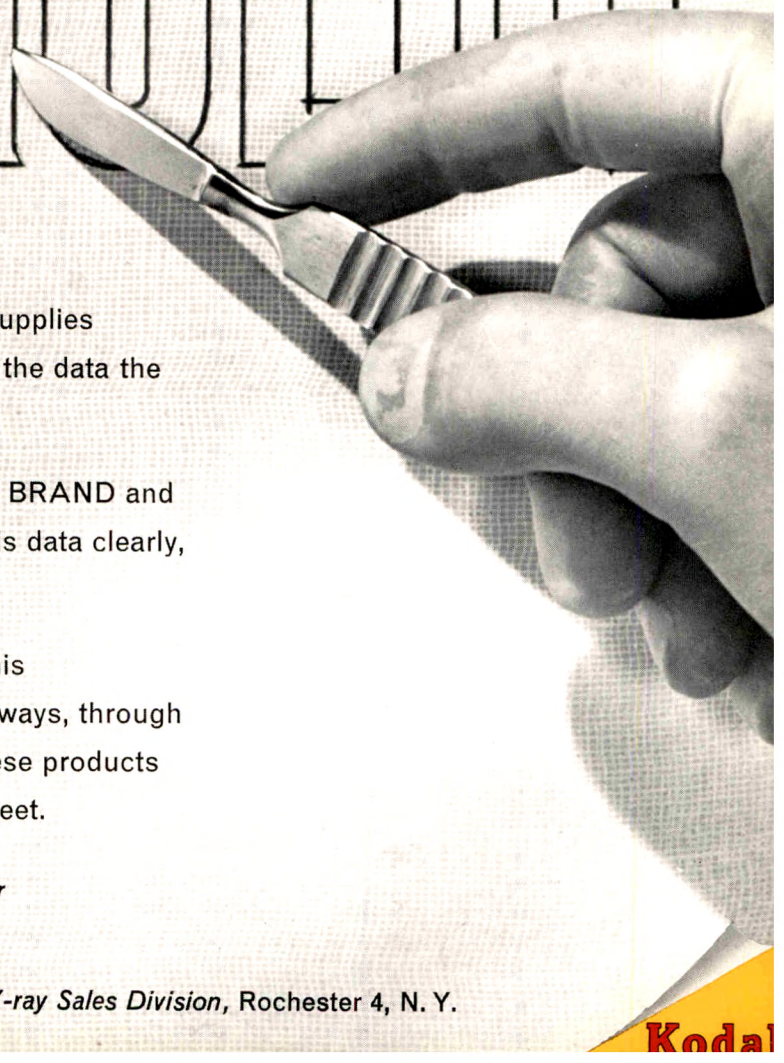
The technique of irradiation remained the same throughout the years, that is, 170 kv., filter 0.5 mm. Zn and 1 mm. Al. In only 16 cases the following factors were different: 140 kv., filter 3 mm. Al. The dose was 50 r every second day up to 150–200 r in younger patients, while in others the dose was 100–150 r every second day for a total of 300–600 r. In older patients the dose was 150–200 r every third day for a total of 700–1,200 r. In a few cases the treatment was repeated a second time but very rarely a third time. The port of entry was generally 8 by 8 cm.

Of the 103 patients who were followed-up, only 97 are alive. The 6 who died expired from 1 month to 5 years after the roentgen therapy, and the cause of death was not related to the thymic lesion nor to the roentgen treatment. In the 97 remaining patients, there was no evidence of neoplastic lesions of the thyroid or of leukemia. In only 1 case, treated at the age of 3 months for thymus hyperplasia, a fibroma of the breast was removed surgically at the age of 13 years.

The follow-up was negative in the 11 cases in whom incomplete data were available.

This article is important because it confirms the point already stressed by other authors that, in the European radiological literature, there are no described cases of cancer of the thyroid following roentgen irradiation of the thymus, while the same cannot be said of the American literature. At this moment, however, there are not enough definite data to think that this difference is due to the largest number of cases treated in the United States or to the different type of technique of roentgen irradiation.—*A. F. Govoni, M.D.*

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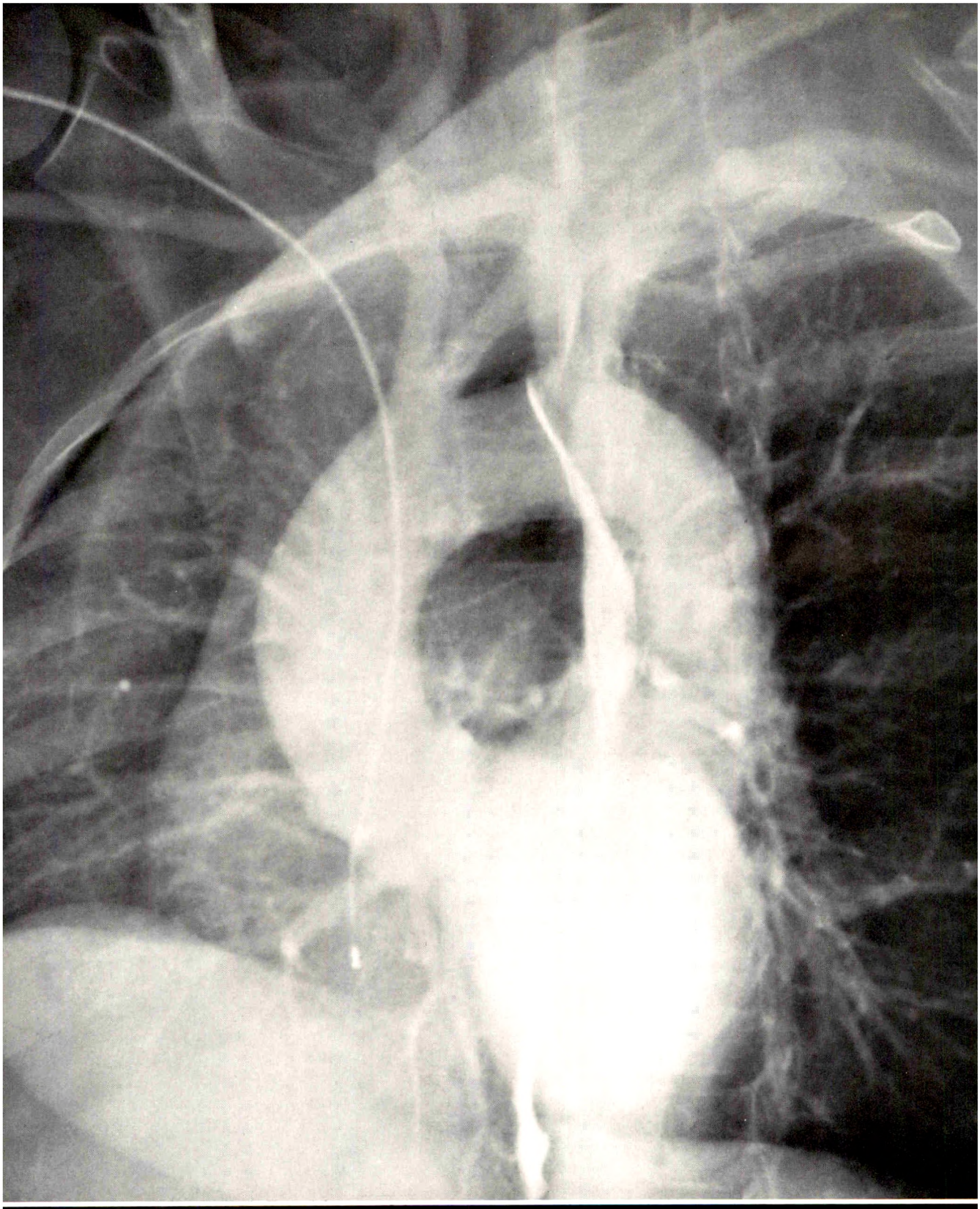
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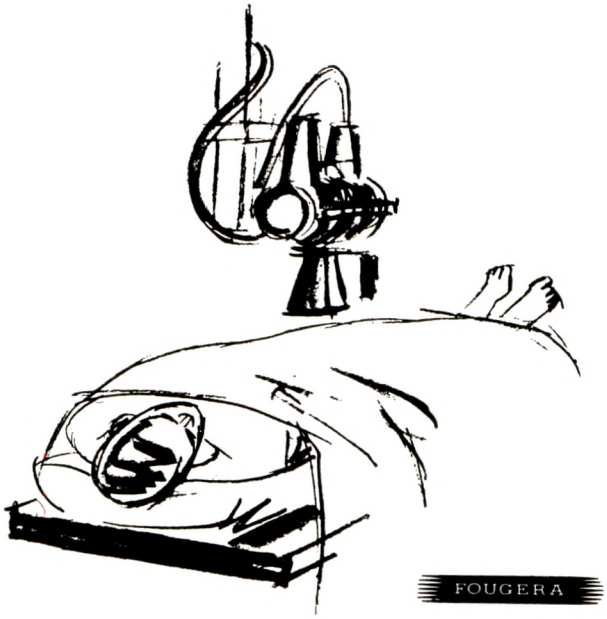
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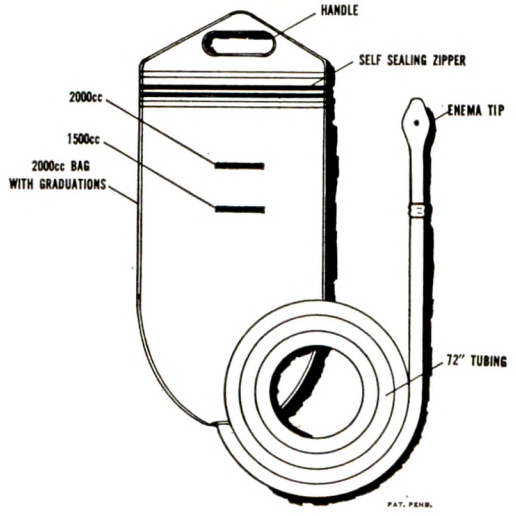
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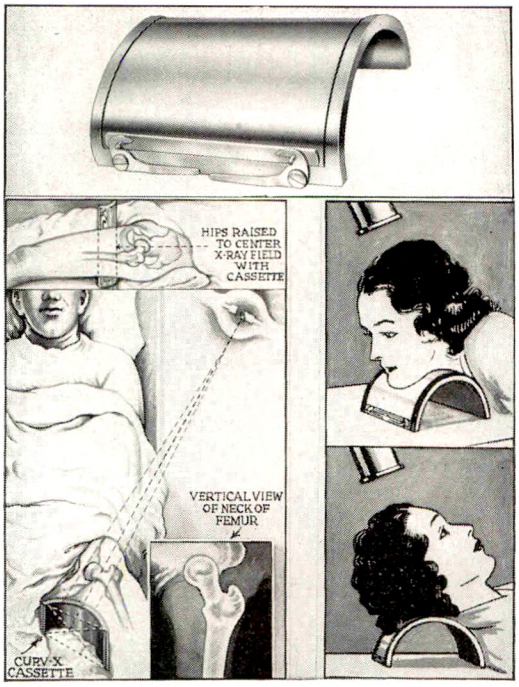
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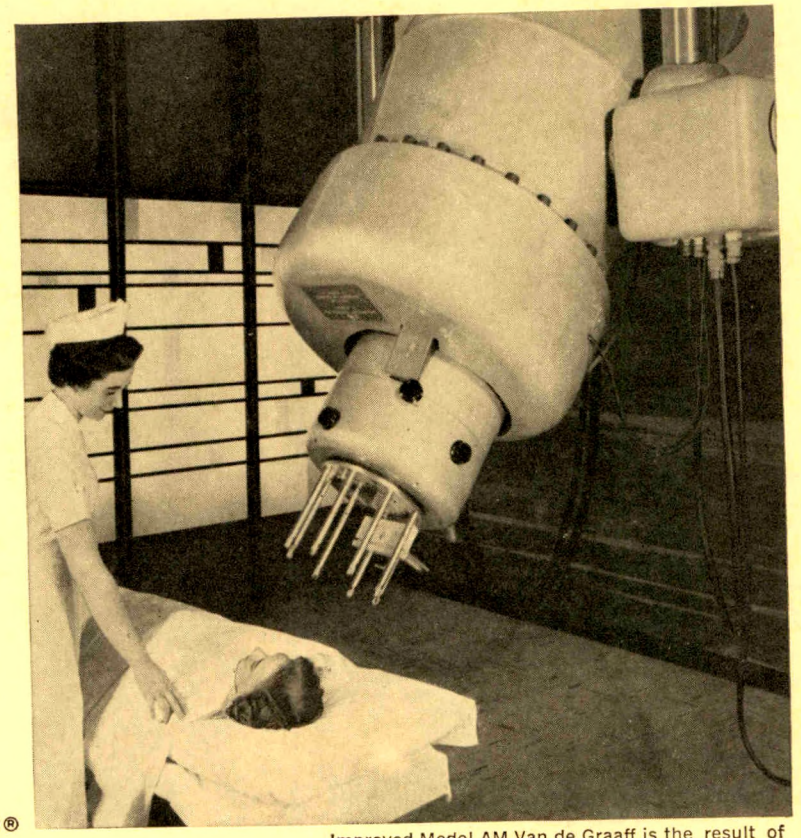
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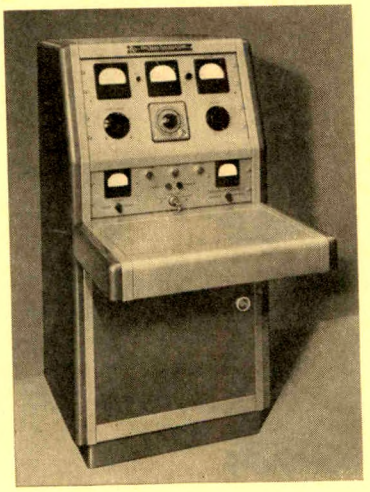


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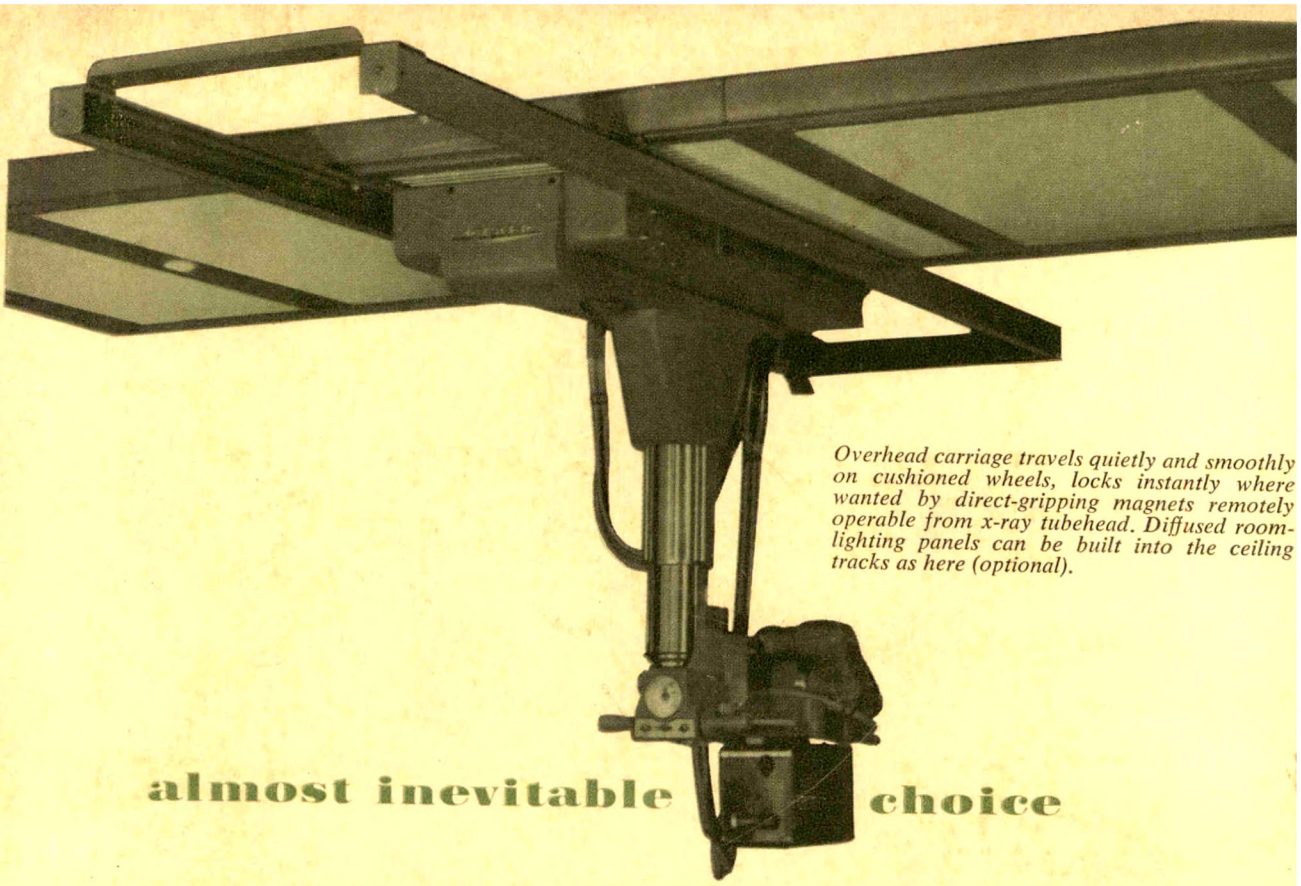


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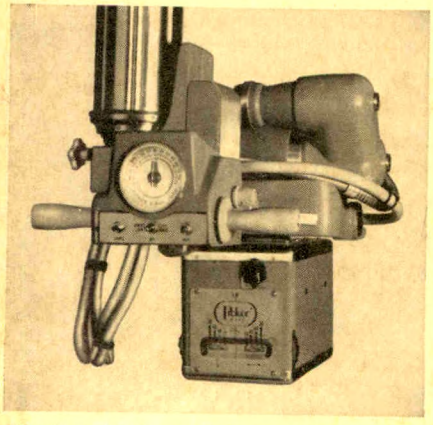
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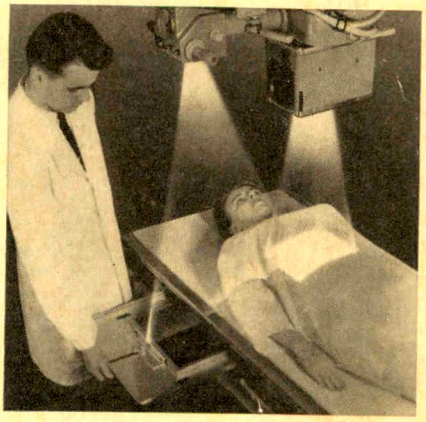
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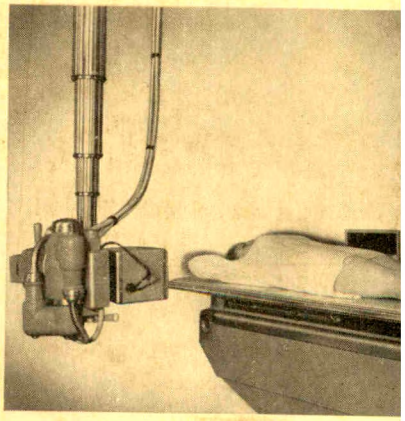
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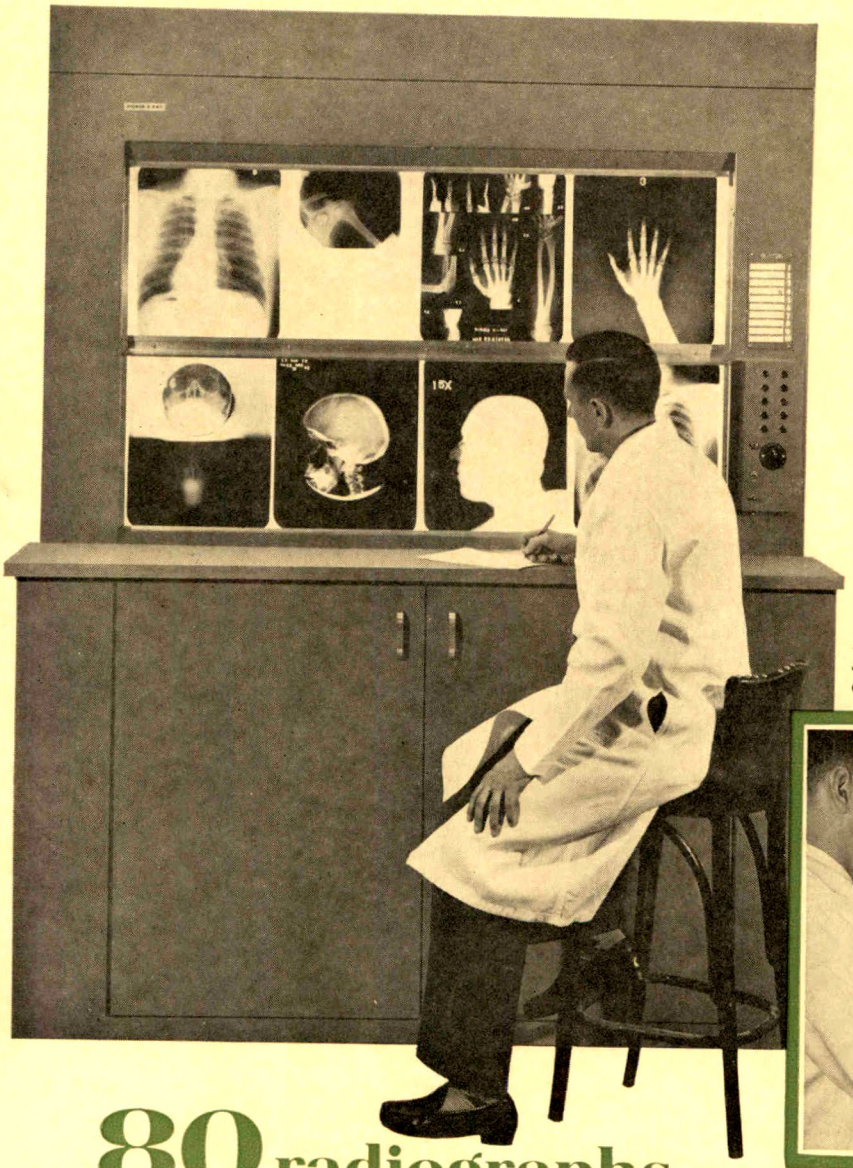


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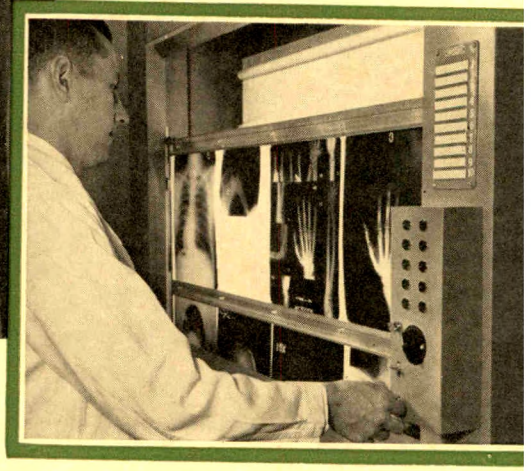
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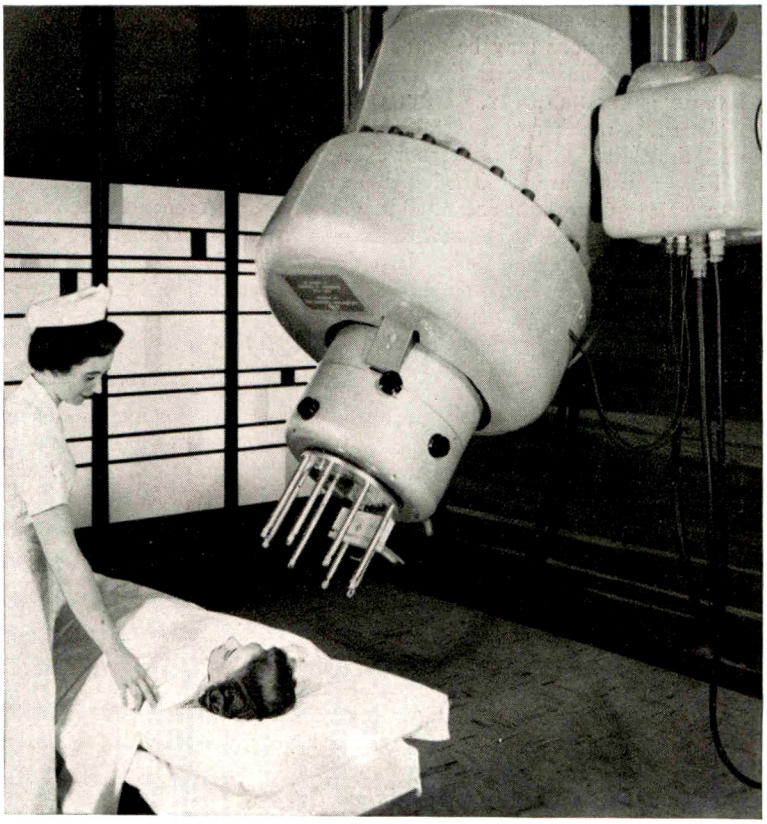
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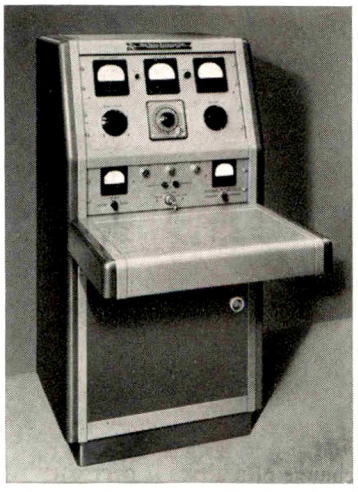


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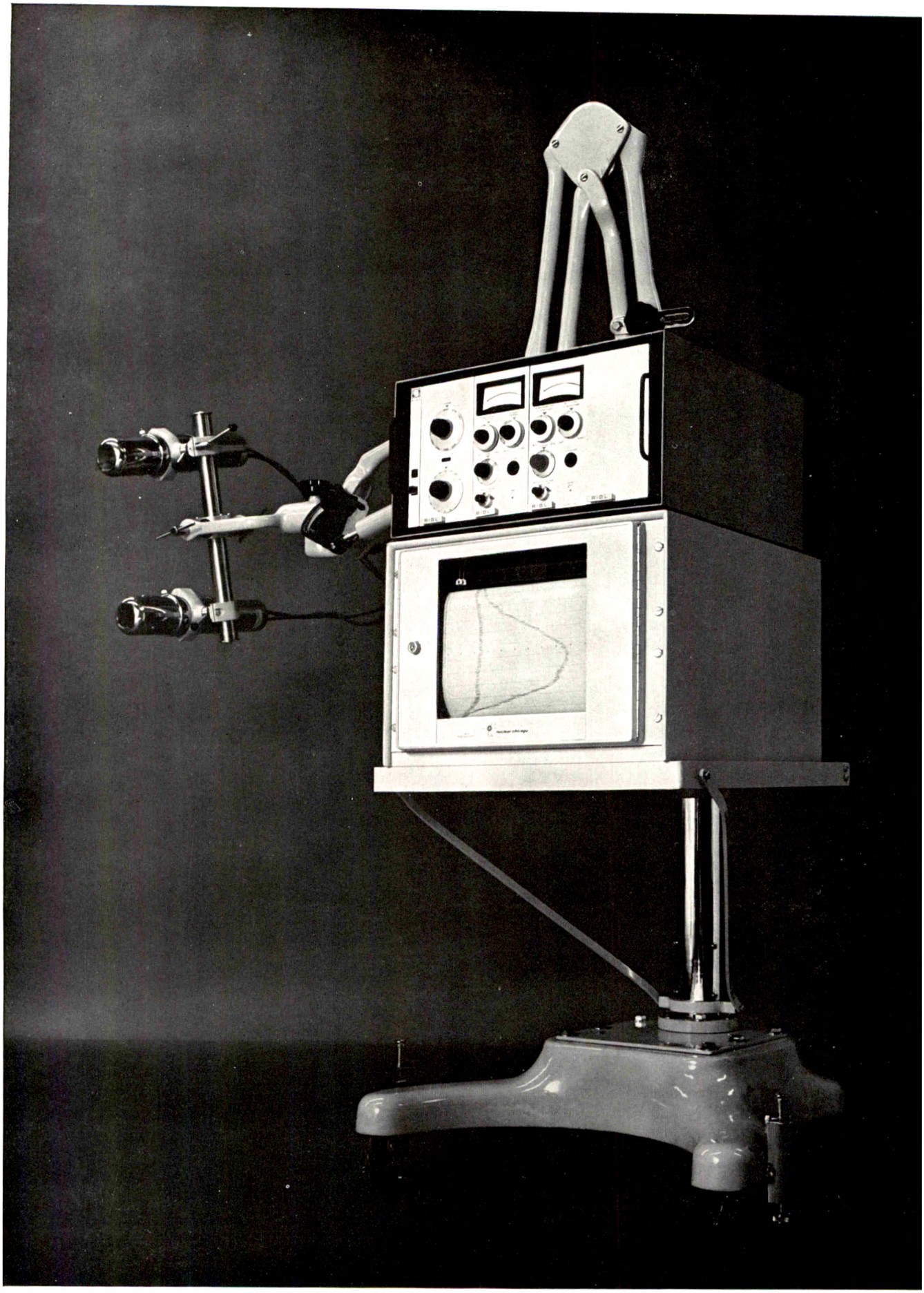
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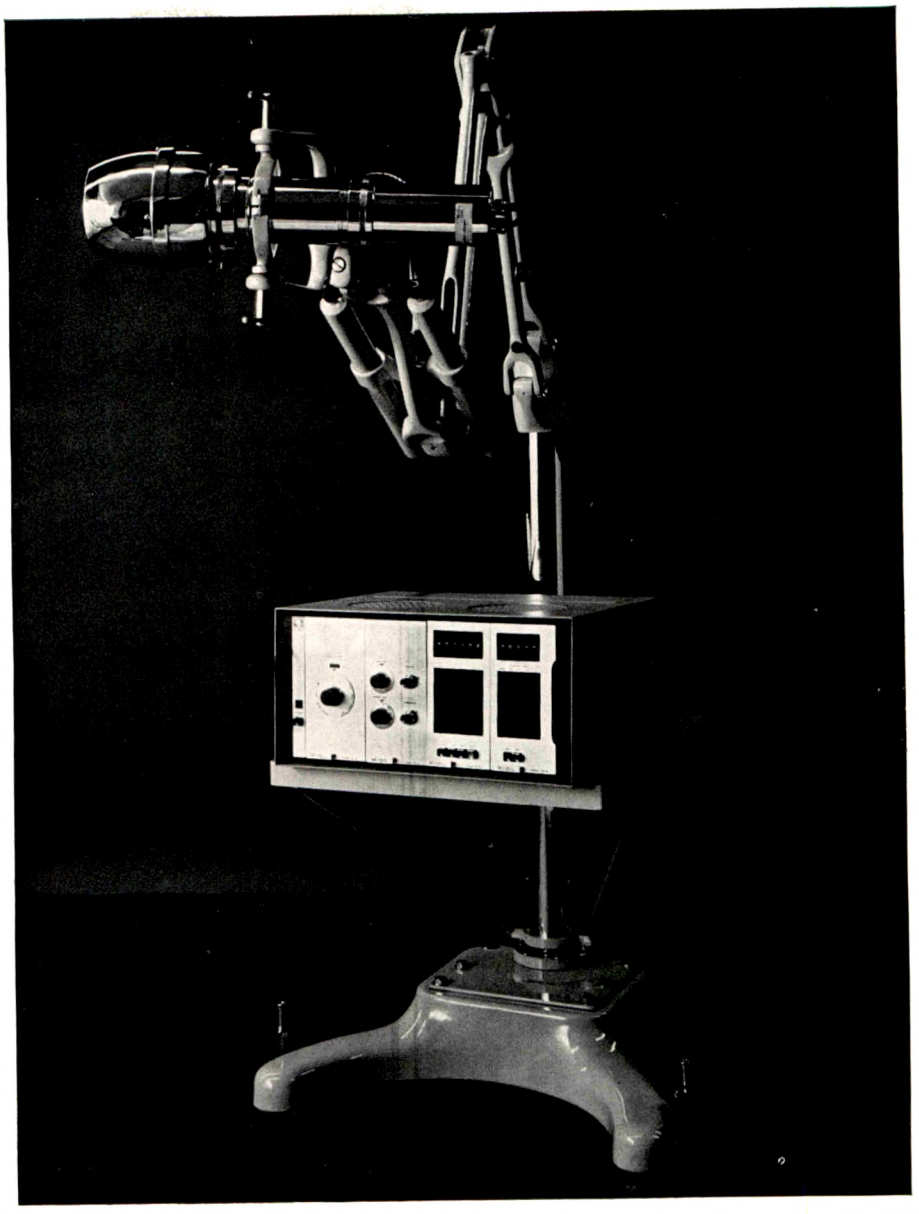
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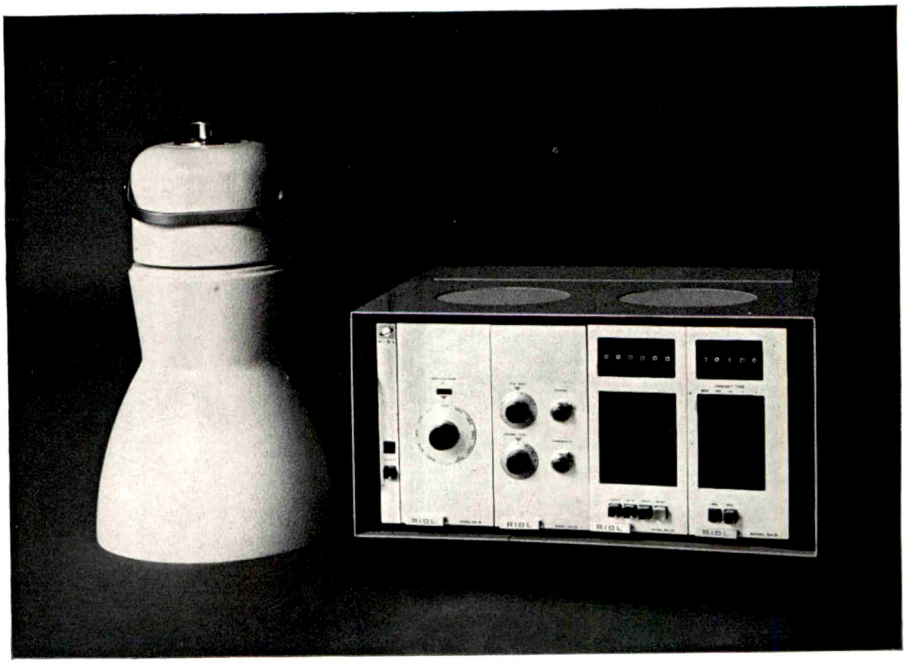
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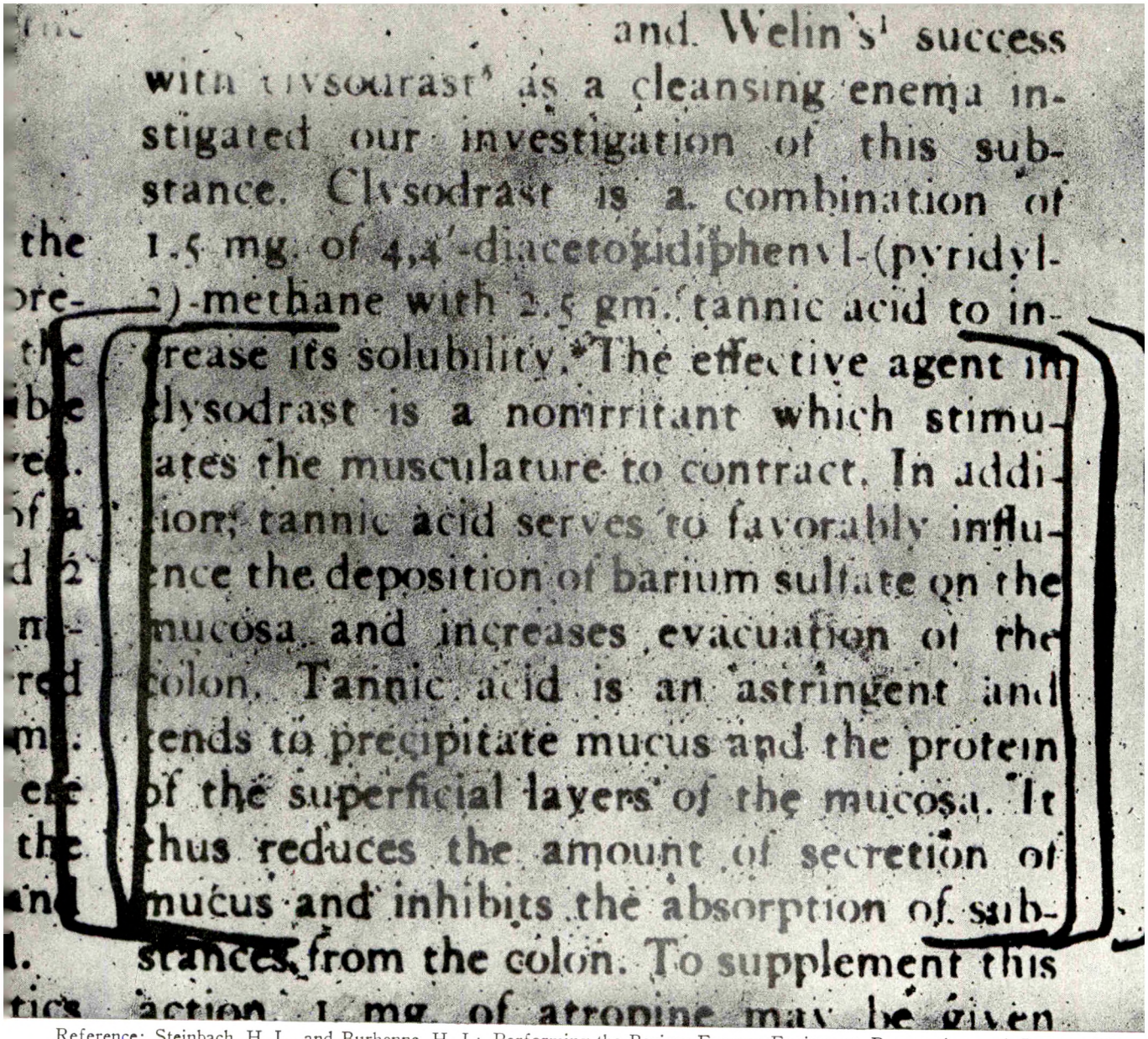


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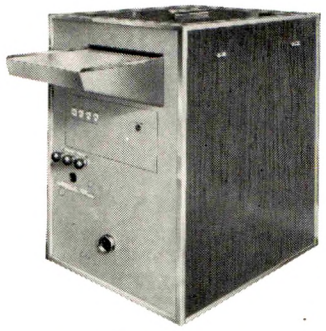
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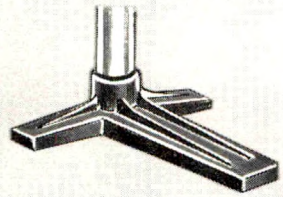
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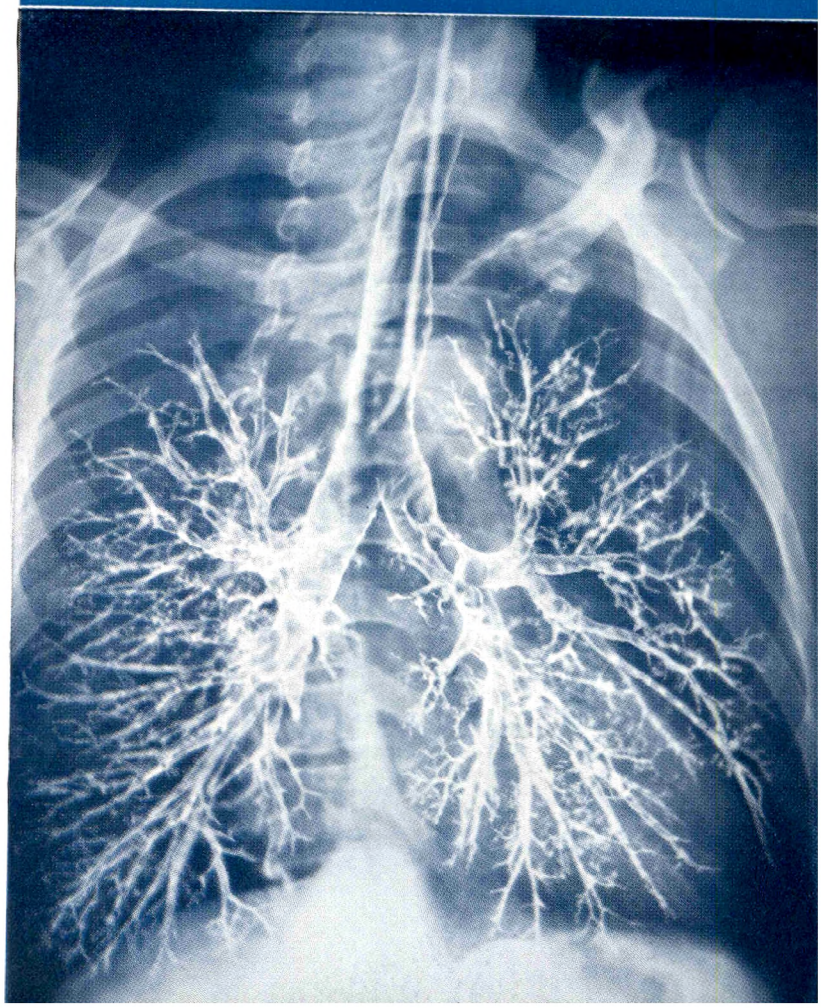
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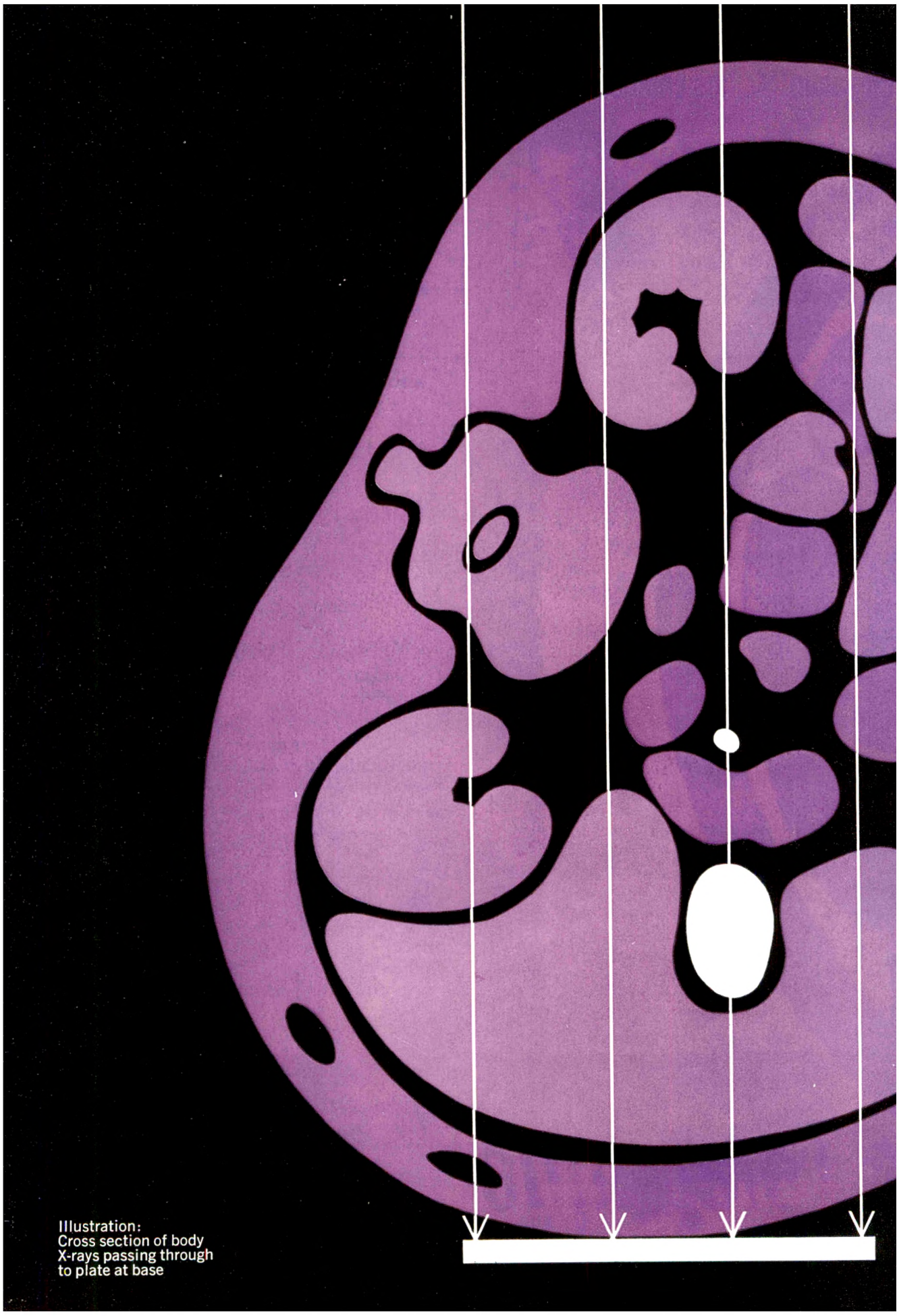


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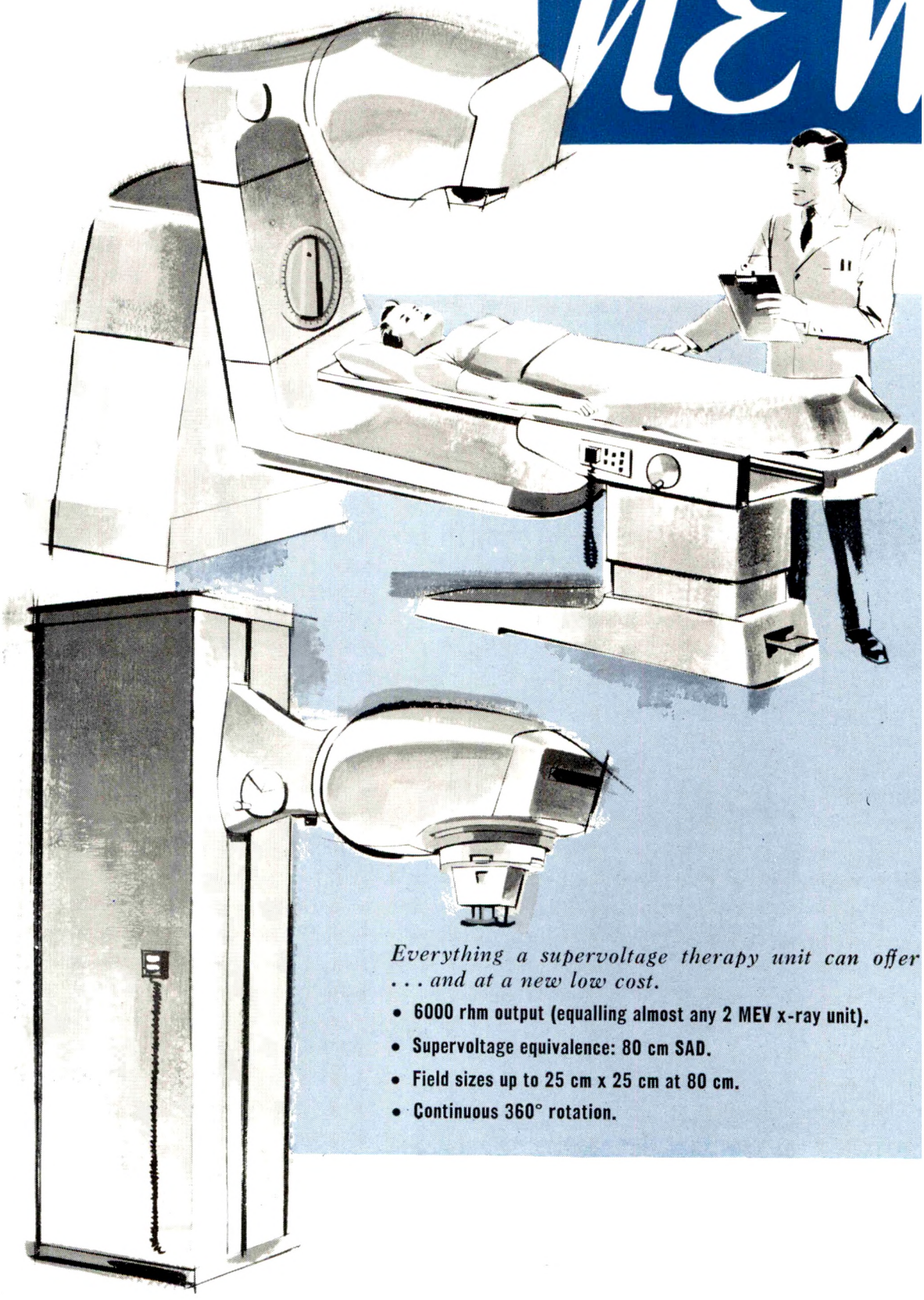
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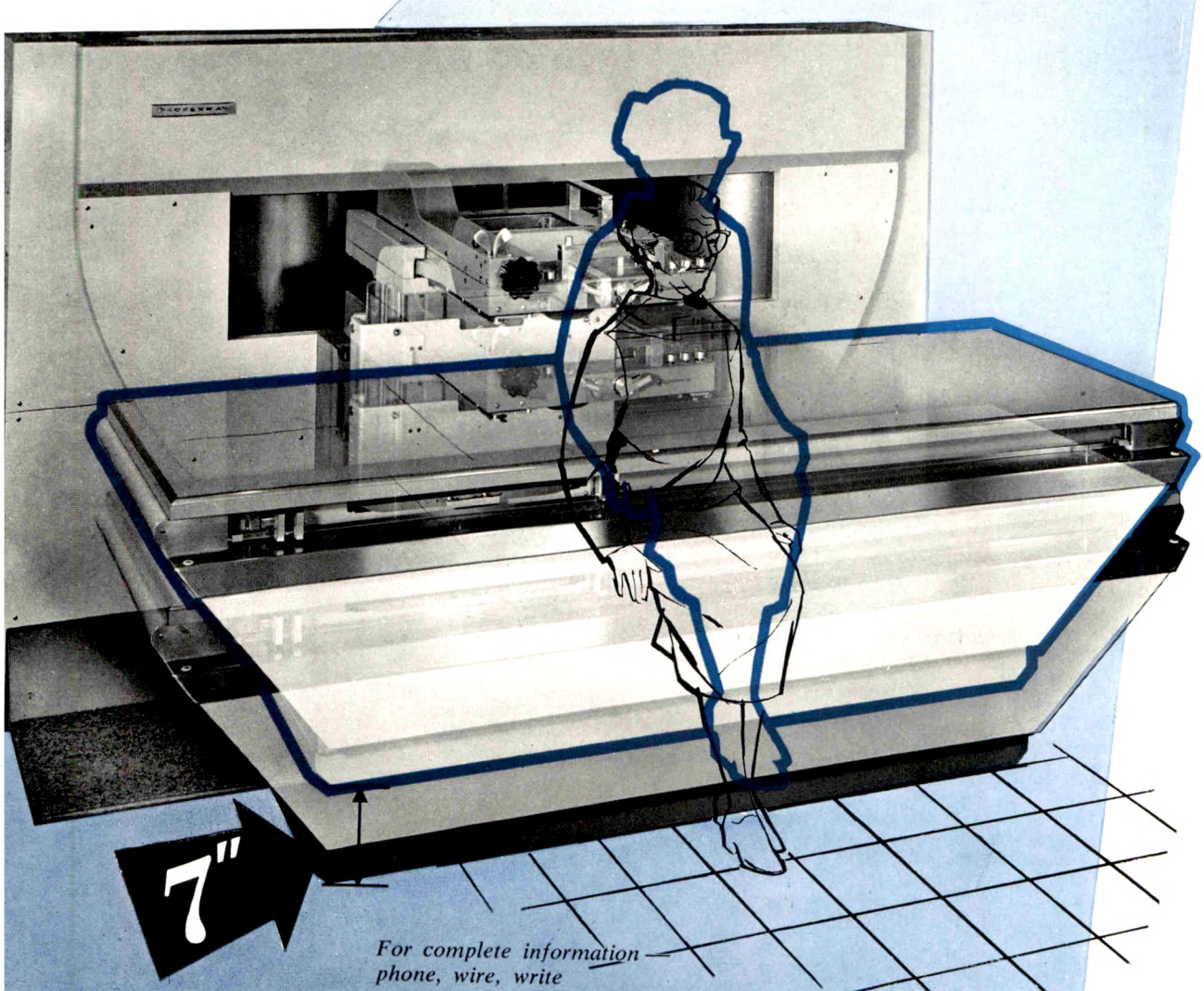
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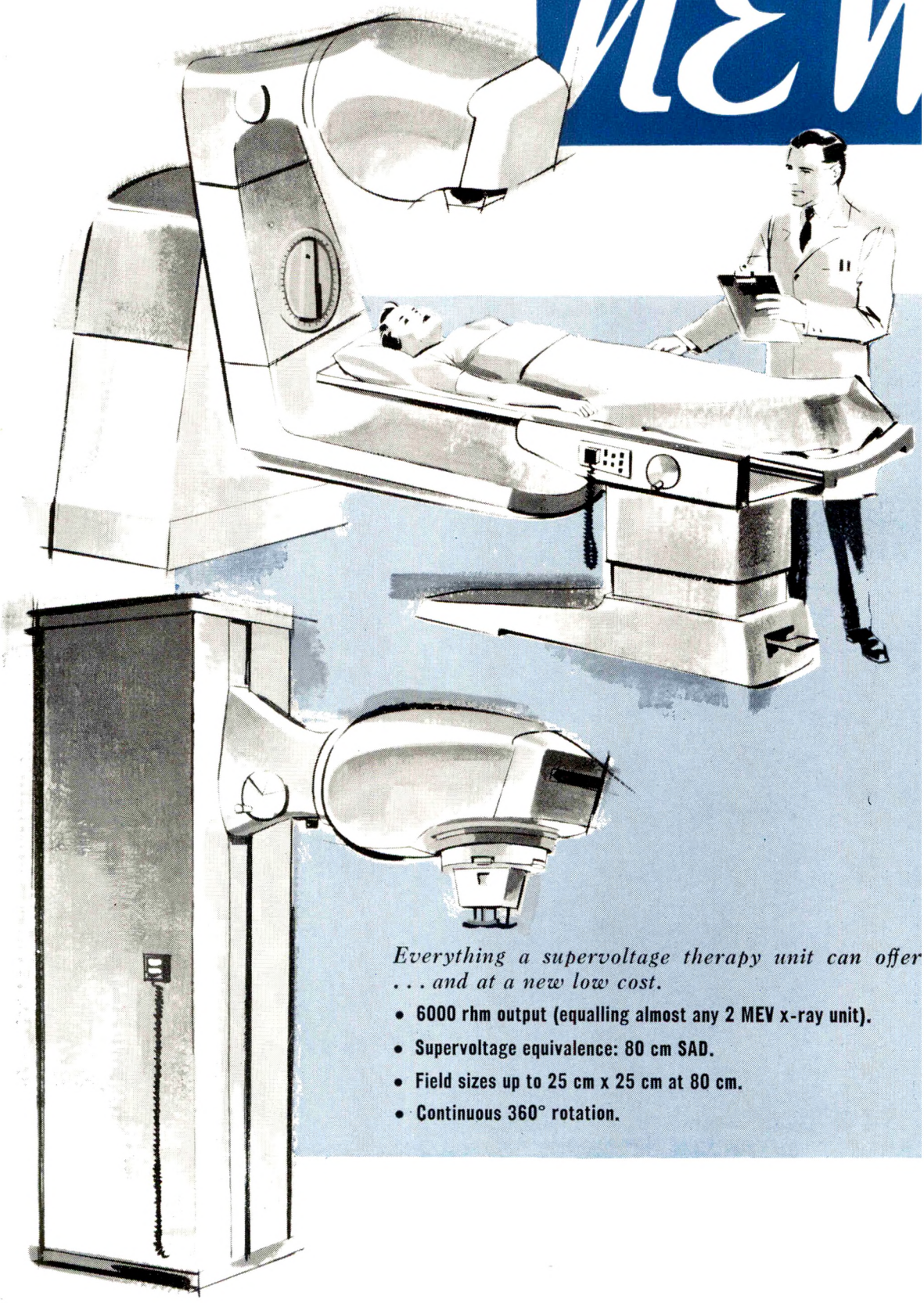
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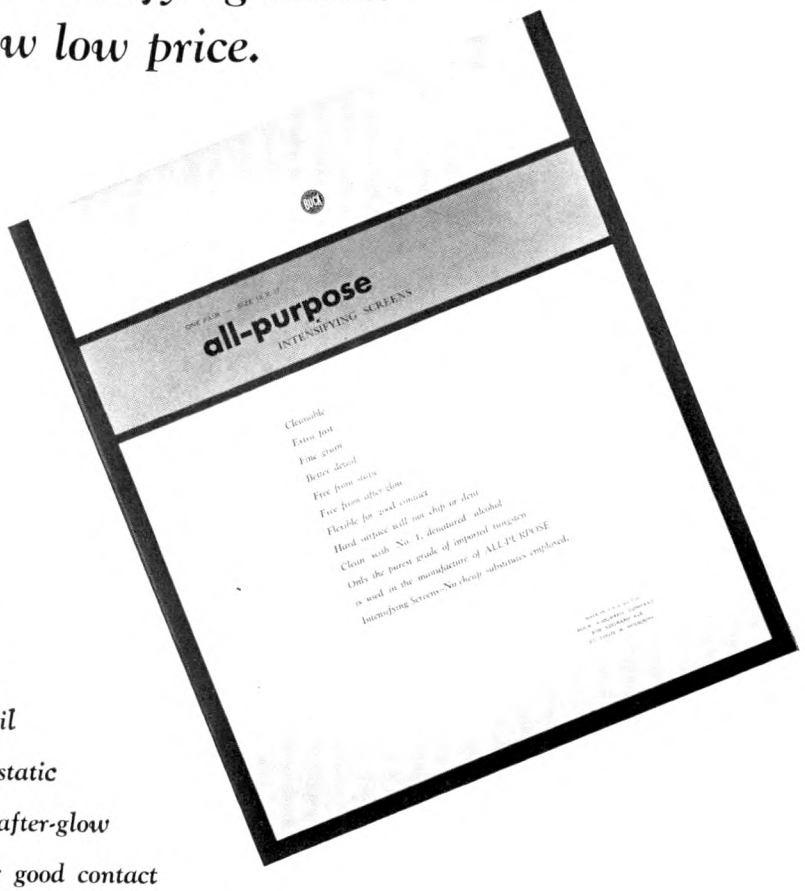
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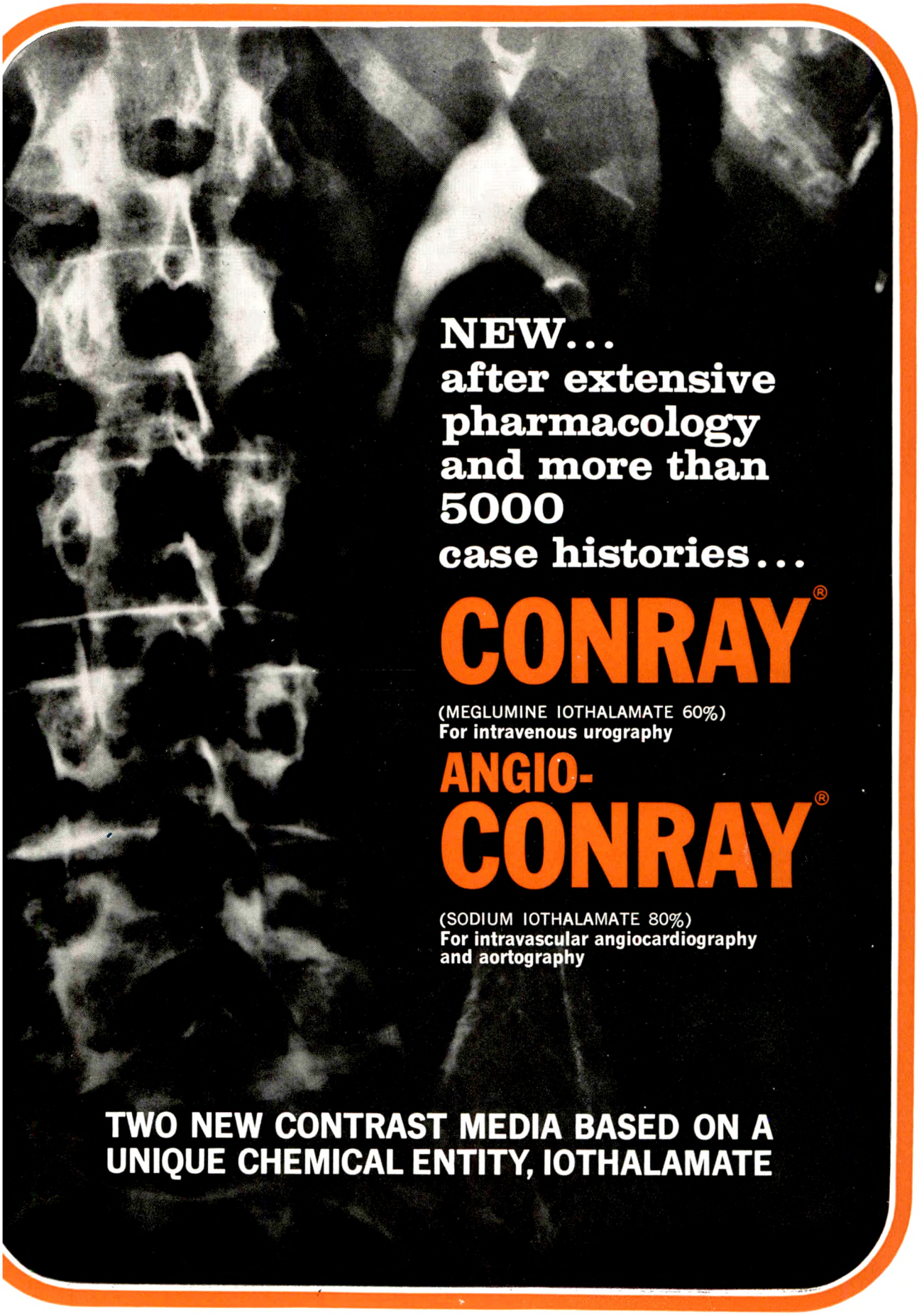
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Pharmacological findings:

A high degree of safety has been demonstrated by the extensive pharmacology conducted on CONRAY and Angio-CONRAY, both salts of the same new compound, iothalamic acid. No attempt is made to summarize all findings here . . . only some important data are presented. A complete bibliography appears on the following pages.

INTRACORONARY INJECTIONS IN DOGS

"Increasing-dose, alternate-injection studies in our laboratory revealed that in dogs there were fewer electrocardiographic changes associated with the intracoronary delivery of [iothalamate] than diatrizoate." [1]

INTRA-AORTIC INJECTIONS IN DOGS

Neurologic responses [2]

	Number of Dogs	Immediate Neurologic Response	Post-Anesthetic Findings			
			Neurologic:		Renal:	
			Paresis	Paraplegia	Azotemia	Necrosis
Sodium iothalamate 80% (Angio-CONRAY)	20	0	0	0	0	0
Sodium and methylglucamine diatrizoates 90%	30	43%	7%	0	0	0

Histological examination of kidneys . . .

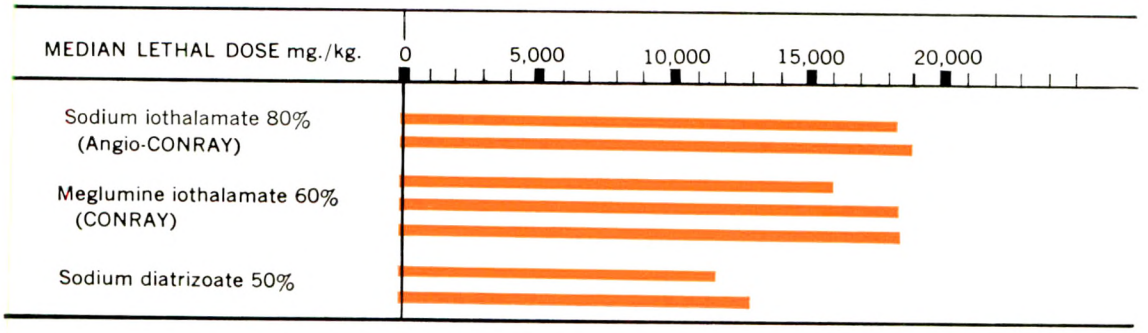
following intra-aortic injection of large doses of iothalamate.

"Microscopic sections of both kidneys of all the dogs [10] were entirely within normal limits. Specifically, there was no evidence of glomerular destruction, tubular damage, casts, or vascular pathology." [4]

Pharmacological findings: (cont'd)

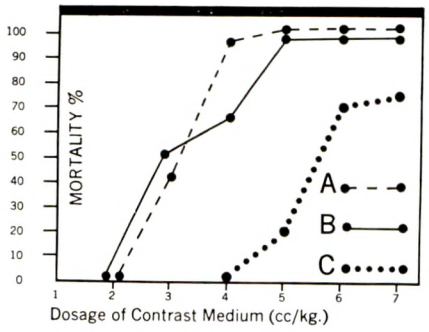
ACUTE TOXICITY

Intravenous LD_{50} in mice [9]



In achieving the acute lethal range in mice and rats, the total volume of undiluted iothalamate solutions administered intravenously *was almost equivalent to the estimated total blood volumes of these animals.* [9]

Intravenous injections in dogs [2,15]



A SODIUM ACETRIZOATE 70%

B SODIUM AND METHYLGLUCAMINE DIATRIZOATES 90%

C [Angio] CONRAY 80%

"Thus the margin of safety in intravenous injections was far greater with Angio-CONRAY." [2]

BLOOD BRAIN BARRIER STUDIES IN DOGS [9,14]

Using a modification of previously reported blood brain barrier tests (Broman and Olsson; Whiteleather; De Saussure), intracarotid injections were made in dogs using 25 cc. of meglumine iothalamate 60% and sodium diatrizoate 50% followed by infusion of Trypan blue dye.

	No. of Dogs	None	Barely Perceptible	Faint	Distinct	Intense
25 cc. meglumine iothalamate 60% (CONRAY)	14	4	3	6	1	0
25 cc. sodium diatrizoate 50%	11	0	0	2	3	6

Even more important than brain staining were the differences in neurological responses when the two media were injected. Dogs receiving sodium diatrizoate (11 dogs) exhibited numerous observable neurological responses such as strong contractions of the neck and thoracic muscles (7 dogs), clonicotonic convulsions and hypersensitivity to sound and touch (9 dogs).

Dogs receiving CONRAY exhibited no convulsions nor hypersensitivity to sound and touch. Four showed slight to mild contractions of the neck and thoracic muscles. The remaining 10 dogs appeared unaffected by the injections.

Clinical commentary:

IN OVER 5000 CASES, [1-3, 6, 7, 12-14, 16, 17]

there has been general agreement among investigators that patient tolerance with iothalamate has been better than that previously experienced with other available agents.

"...The intravenous injection of /CONRAY/ for urography is practically devoid of unpleasant reaction." **STEINBERG, I. and EVANS, J. A.**[16]

"In view of its several distinct advantages, it is likely that iothalamate will supersede presently available agents for cardiovascular contrast visualization." **STRAUBE, K. R. and DOTTER, C. T.**[17]

"At the present time, Angio-CONRAY would appear to be the concentrated angiographic medium of choice." Foster, et al. further state that "experimental studies clearly demonstrated that sodium iothalamate is the least toxic angiographic contrast medium yet tested." **FOSTER, J. H., et al.**[2, 3]

"If further clinical experience confirms our impression of its relative safety and freedom from side effects, /iothalamate/ will, in fact, warrant the term 'drug of choice'—at least until a better preparation is found." Citing the importance of the need for rapid delivery of concentrated contrast media through small bore catheters, Dotter, et al. further observed that "...from this point of view, /iothalamate/ is an outstanding medium." **DOTTER, C. T., et al.**[1]

"Clinical experience with a new concentrated contrast agent, Angio-CONRAY, in angiocardiography, nephrotomography, intravenous aortography, and retrograde renal arteriography indicates that the usual reaction was mild and transient, and was well tolerated. Low viscosity and ready solubility of Angio-CONRAY permit ease and speed of injection. These factors, together with good contrast visualization, make Angio-CONRAY a preferable contrast medium for angiographic procedures." **KANICK, V. and FINBY, N.**[7]

"Angio-CONRAY is the agent of choice for aortography and angiocardiography. CONRAY is the preferred agent for intravenous urography... It appears that the compound is more rapidly excreted than the other common opaques and maximum density of contrast is evident in five minutes." **MARSHALL, M. D. and LING, J. T.**[13]

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1. Dotter, C. T.; Straube, K. R.; Bilbao, M. K., and Hinck, V. C.: New Contrast Medium for Intravascular Use, Northwest Med. *61*:41-6 (Jan.) 1962. 2. Foster, J. H.; Sessions, R. T.; Winfrey, E. W.; Killen, D. A., and Collins, H. A.: Clinical and Experimental Evaluation of Angiographic Contrast Media, Scientific Exhibit presented at the 111th Annual Meeting of the American Medical Association, Chicago, Illinois, June, 1962. 3. Foster, J. H.; Winfrey, E. W.; Killen, D. A., and Sessions, R. T.: A New and Superior Angiographic Contrast Medium, Sodium Iothalamate 80%: A Clinical and Experimental Evaluation. To be published. 4. Bernstein, E. F.; Mackey, G. C.; Emmings, F. G., and Amplatz, K.: Experimental Evaluation of Renal and Spinal Cord Tolerance to a New Angiographic Agent, Angio-CONRAY, Surgery *51*:663-7 (May) 1962. 5. Bernstein, E. F.; Reller, C. R., and Grage, T. B.: Experimental Studies of Angio-CONRAY: A New Angiographic Agent, Radiology. To be published. 6. Dotter, C. T.; Straube, K. R.; Bilbao, M. K., and Hinck, V. C.: An Initial Report on Iothalamate. A New Contrast Agent for Intravascular Administration, Scientific Exhibit presented at the Annual Meeting of the Radiological Society of North America, Chicago, Illinois, November, 1961. 7. Kanick, V., and Finby, N.: Angio-CONRAY: A New Angiographic Contrast Agent. To be published. 8. Killen, D. A.; Foster, J. H., and Scott, H.W., Jr.: Toxic Reactions Incident to Urokon Aortography as Related to the Volume of Contrast Medium Injected. Addendum.

Physical characteristics:

Iothalamate is a new chemical entity synthesized and developed by Mallinckrodt Pharmaceuticals. It is chemically identified as 5-acetamido-2, 4, 6-triiodo-N-methylisophthalamate. CONRAY is an aqueous solution of meglumine iothalamate at 60% concentration. Angio-CONRAY is an aqueous solution of sodium iothalamate at 80% concentration.

Both in iodine content and viscosity, Angio-CONRAY is superior to comparable diatrizoates. It has the highest iodine content (48%) of any available contrast medium, and its viscosity is almost 3 times lower than comparable diatrizoates.



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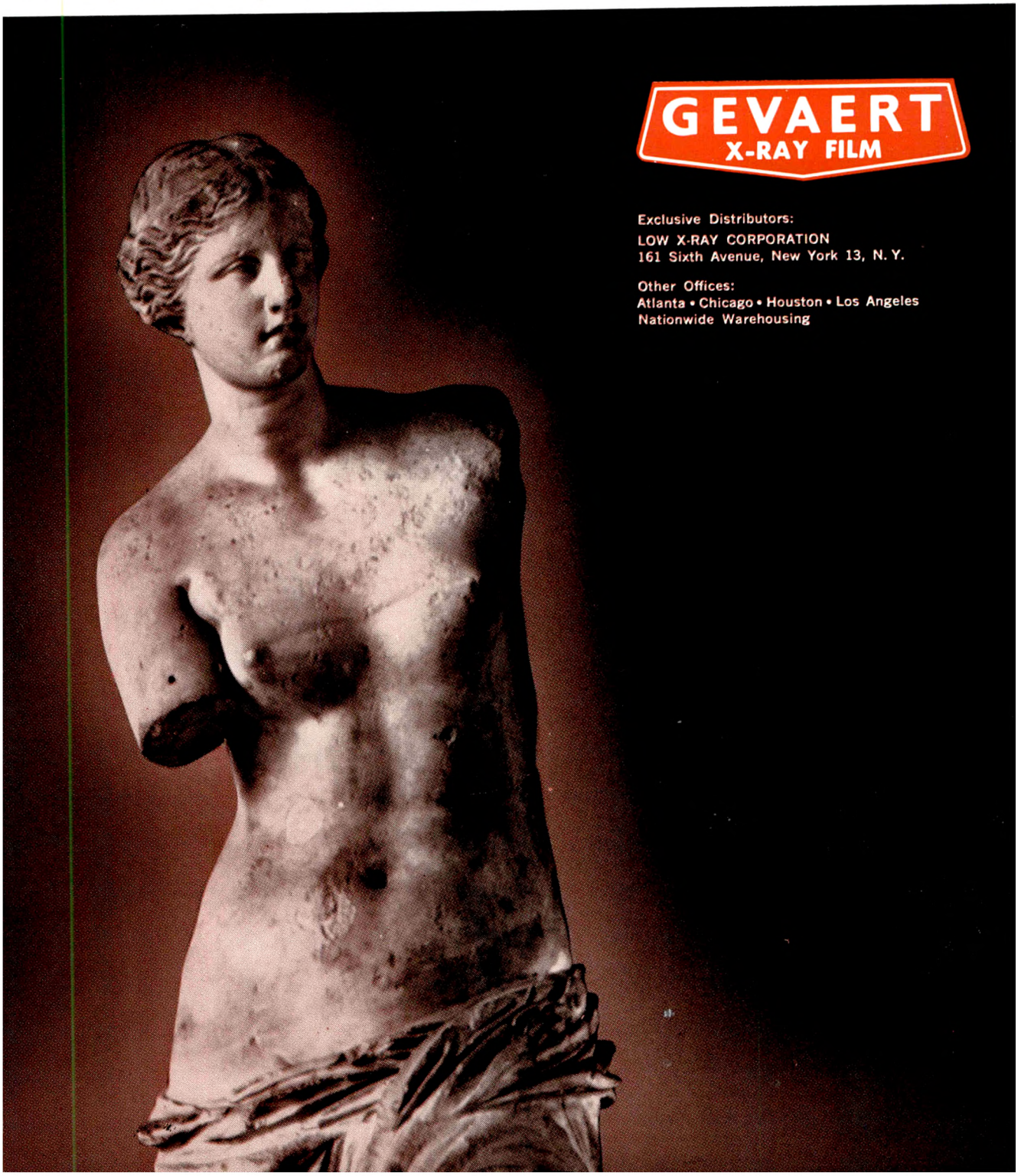
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THE VALUE OF THE "SILHOUETTED" VIEW

by Justin J. Wolfson, M. D., Radiologist
Irel Fred Atencio, R. T.
Bernalillo County-Indian Hospital
2211 Lomas Boulevard, N. E.
Albuquerque, New Mexico

The Conventional examination for the ribs, as described in standard reference texts, consists of PA and AP and both oblique views. The Left Anterior Oblique is used for injury to the right rib cage and the Right Anterior Oblique for injury to the left rib cage.

Frequently a rib fracture or other lesion of the rib cannot be demonstrated by this technique, and for good reason: the method is incorrect.

The rib cage is a cylindrical structure. Thus a lesion of the rib will best be demonstrated if the central ray is tangential to it. In our department we refer to this as "silhouetting" or "lateralizing" the lesion. For example, suppose we have a fracture of the left fifth rib anteriorly, as shown in figure 1, point (a). In order to secure the best possible visualization we must rotate the rib cage, as shown in figure 1b or 1c, until point (a) has been "lateralized." On the other hand, if the fracture is posterior rather than anterior, though still on the left, we must rotate the patient in the opposite direction, as shown in figure 2b or 2c, point (b). The purpose is still the same—to silhouette the lesion.

(Continued on back)

Figures 1 and 2—In figure 1 the patient is lateralized until the point of greatest tenderness or area of the lesion located anteriorly is lateralized. In figure 2, though the lesion is on the same **side** as in figure 1, the patient is turned in the opposite direction. This is because the lesion lies **posteriorly.**

Figures 1c and 2c represent variations of figures 1b and 2b and are sometimes to be preferred.

Thus, the decision as to which way to rotate the patient depends on whether the lesion is **posterior** or **anterior** and not on the side it is on.

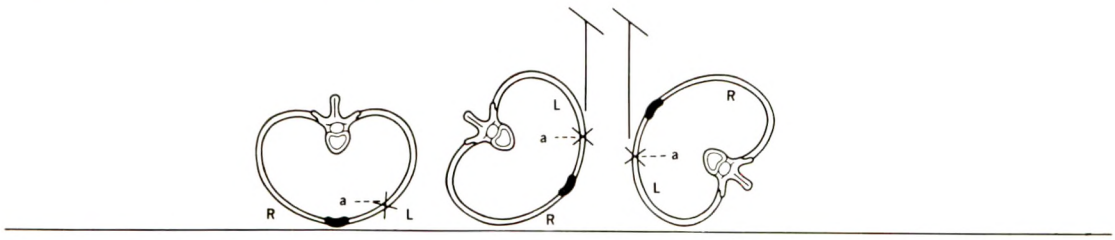


Fig. I (a) Fig. I (b) Fig. I (c)

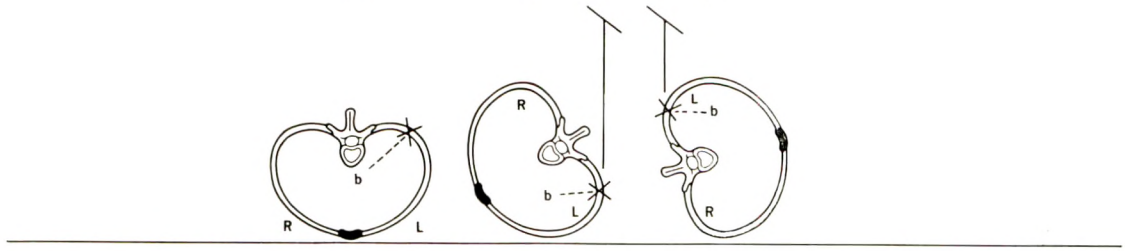


Fig. II (a) Fig. II (b) Fig. II (c)

OVER



Figure 3—A silhouetted or lateralized view revealing clearly a rib fracture and extrapleural thickening. The fracture could not be seen on a conventional view.

This method is particularly valuable for delineating a fracture or other lesion which is close to the transverse process or costocartilagenous junction.



Figure 4. (Skull)—This film demonstrates a fracture of the external table of the skull. The area of injury was silhouetted. The regular films of the skull, though of excellent quality, did not demonstrate a fracture.

Thus, according to the concept of silhouetting a lesion, the decision as to whether to rotate a patient to the right or to the left is determined not by what side the lesion is on (as in the conventional approach) but by whether it lies anteriorly or posteriorly. Here is a description of our method for rib fractures: (Of course, it can be modified to suit any type of rib lesion.)

The examination consists of an AP or PA view of the rib cage plus an especially positioned oblique. Our technique for taking the oblique is as follows:

The patient is asked where he hurts. The rib cage is carefully palpated. A letter "X" is placed on the skin in the center of the area of greatest tenderness. (Occasionally more than one mark is made.) Upright or lying, PA or AP, the patient is turned until the letter "X" is rotated as far laterally as possible. The fracture, if present, is now silhouetted. The "X" is centered to film tube. A coned-down view is now taken. (See figure 3)

OTHER USES:

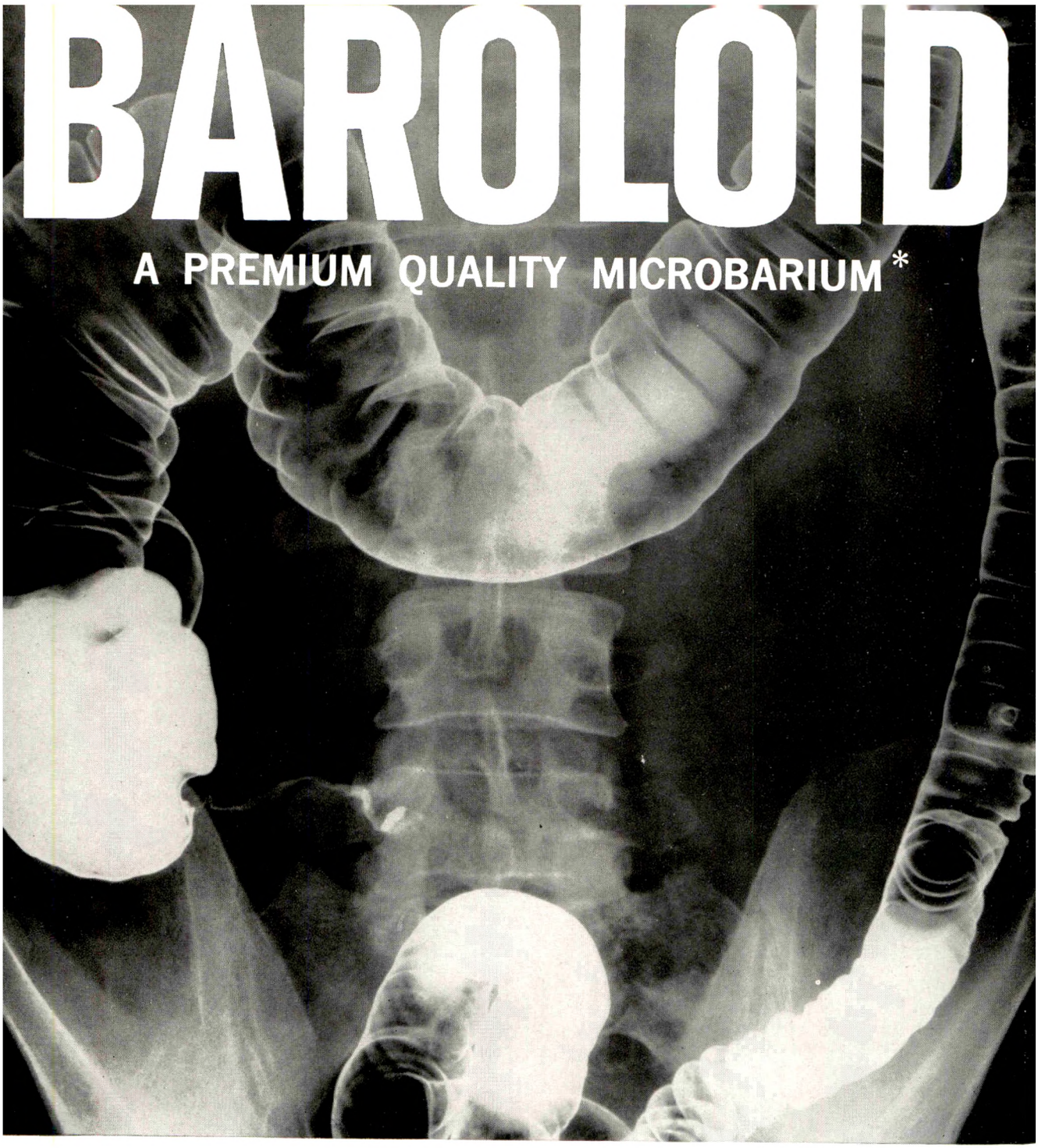
Since much of the body is cylindrical, this technique has many applications. Some examples are as follows:

a) Lesions of the skull (see figure 4), pelvis, or long bones.
b) Lesions of the body of the stomach, e.g., to silhouette induration about an ulcer crater.

SUMMARY:

(1) The method of "silhouetting" a lesion is described particularly as it applies to fractures and other lesions of the ribs and skull.
(2) The method is practical. In the long run it conserves both time and film and leads to much greater accuracy in diagnosis.

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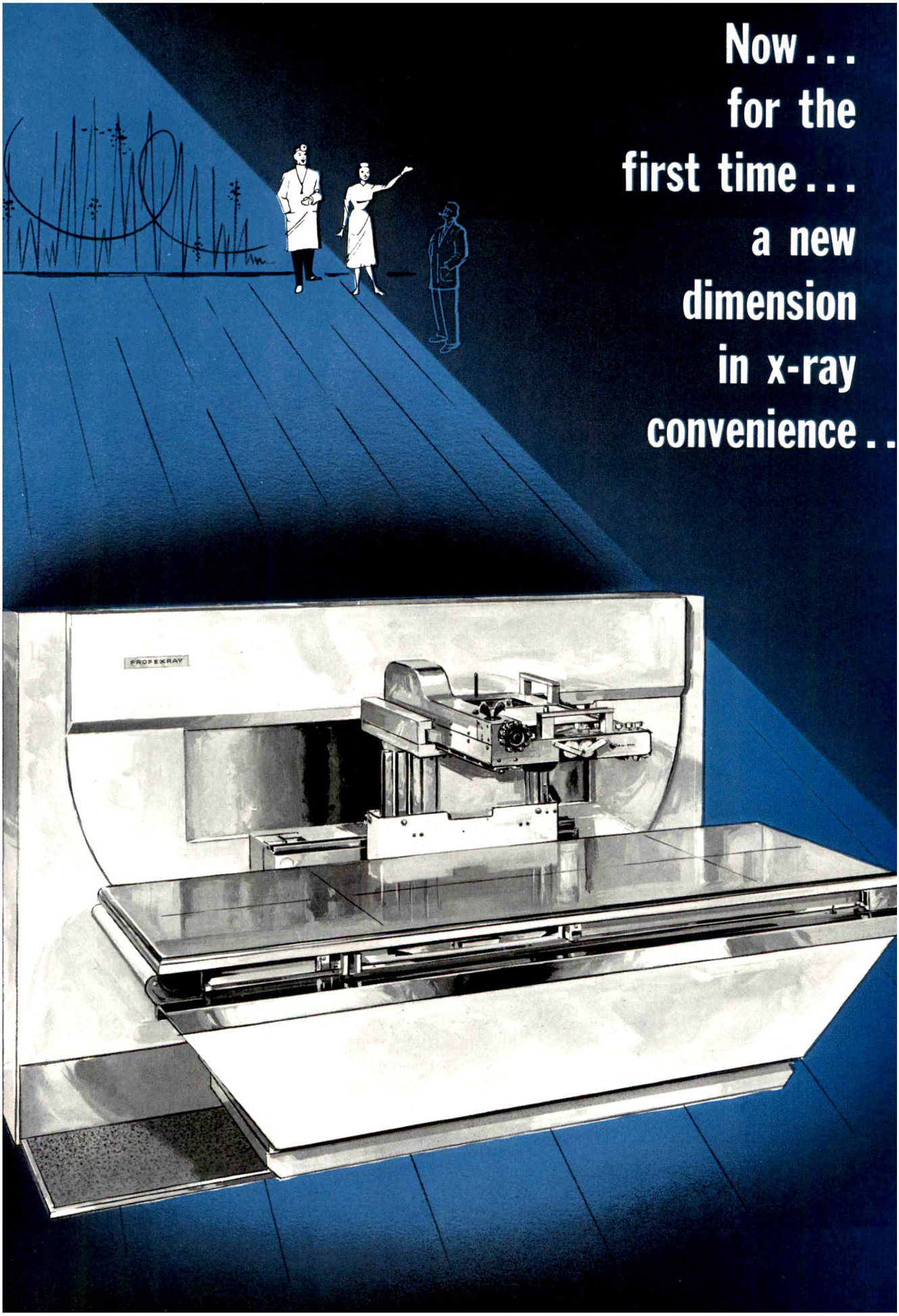
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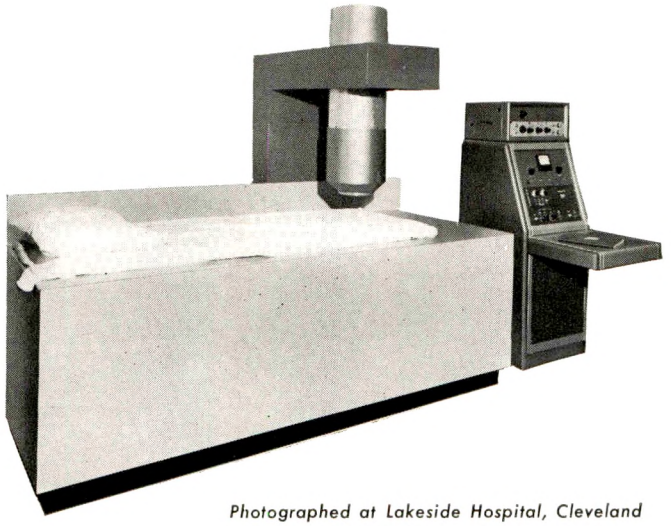
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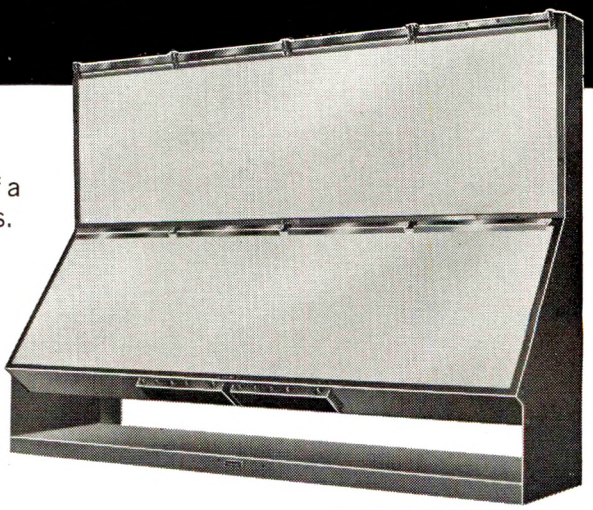
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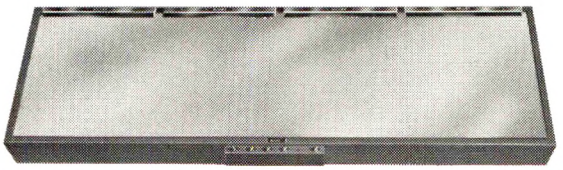
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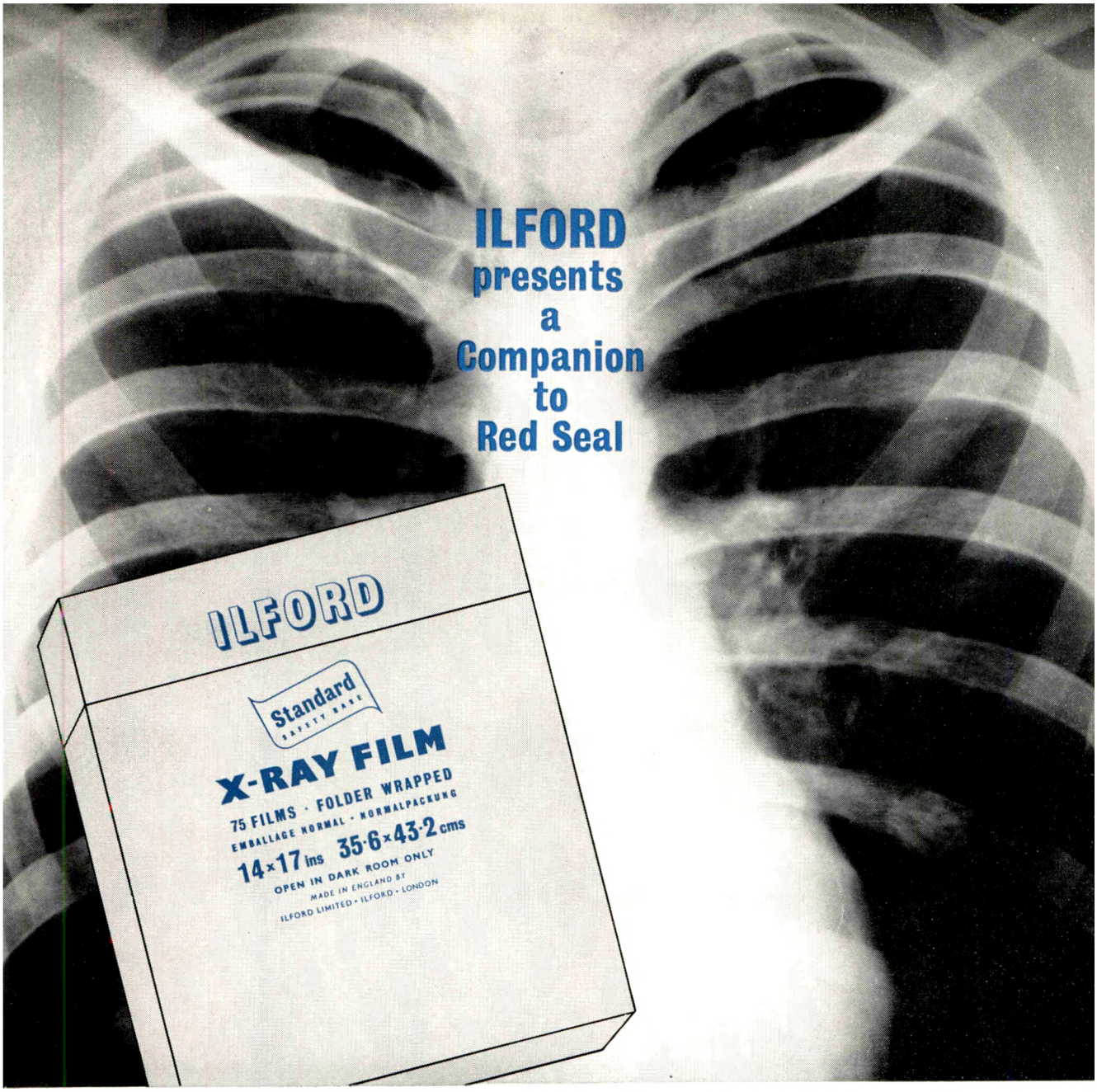
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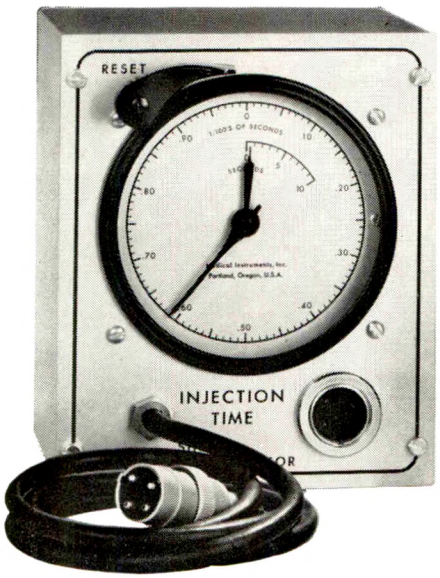
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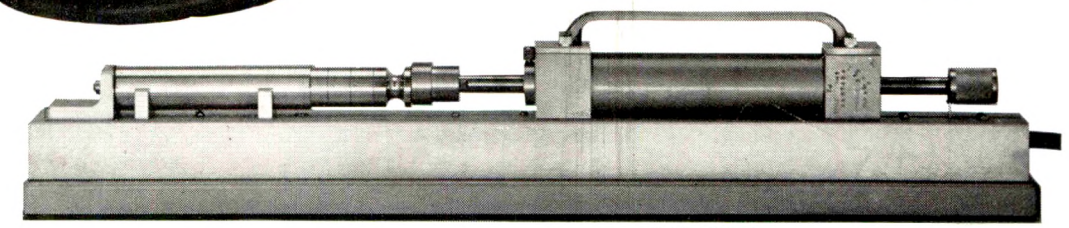
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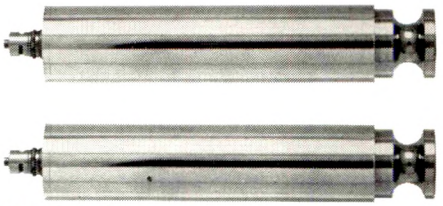
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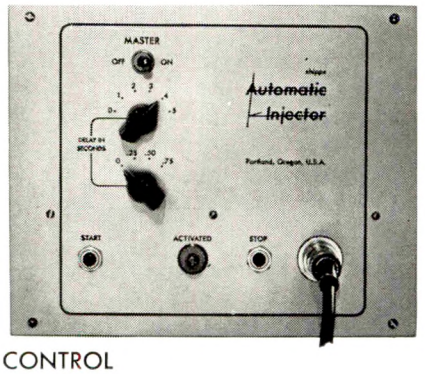
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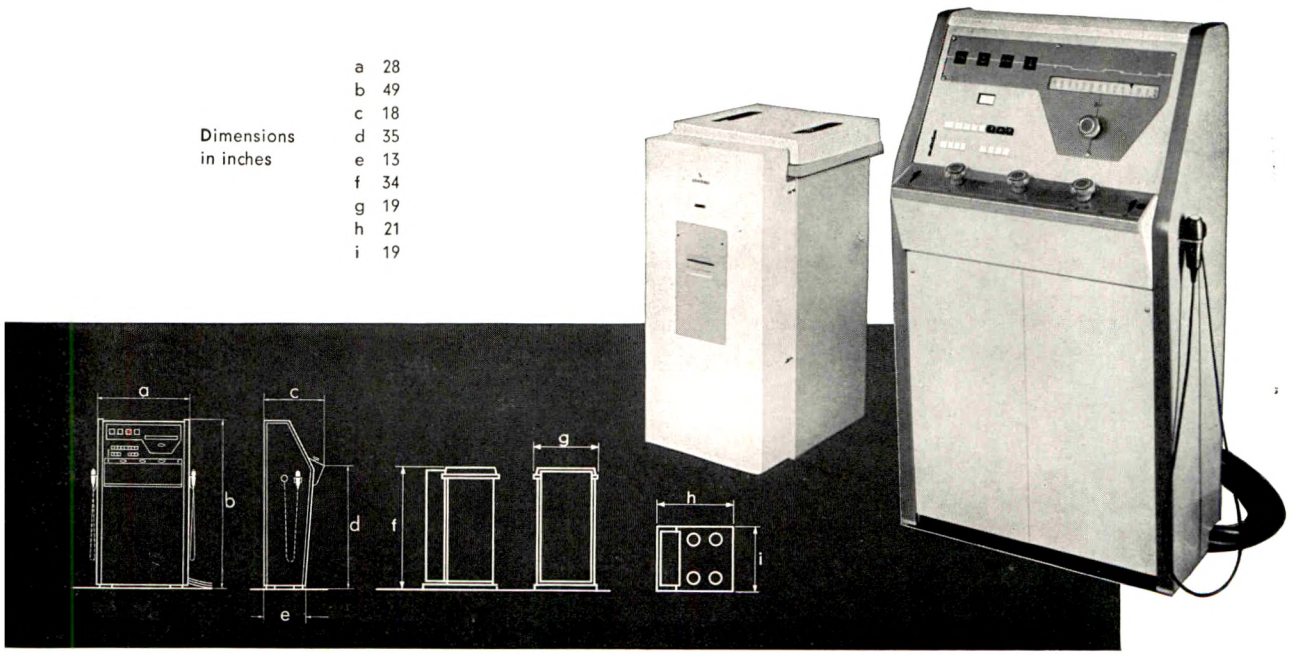
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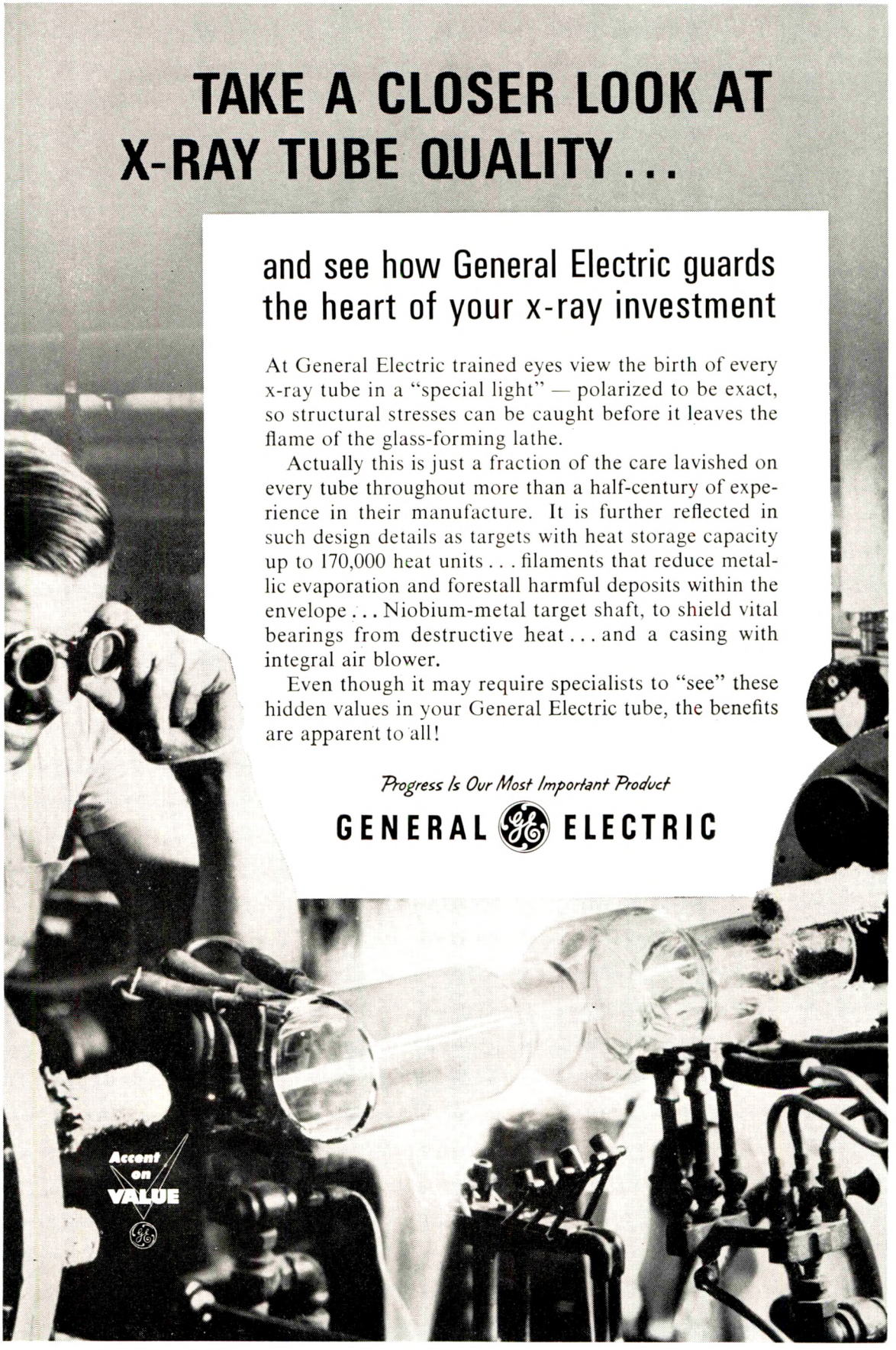
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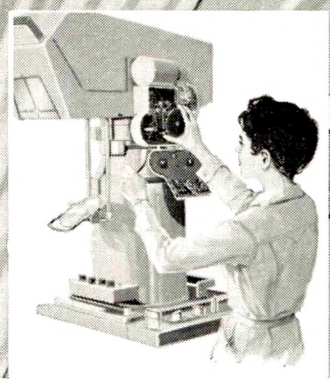
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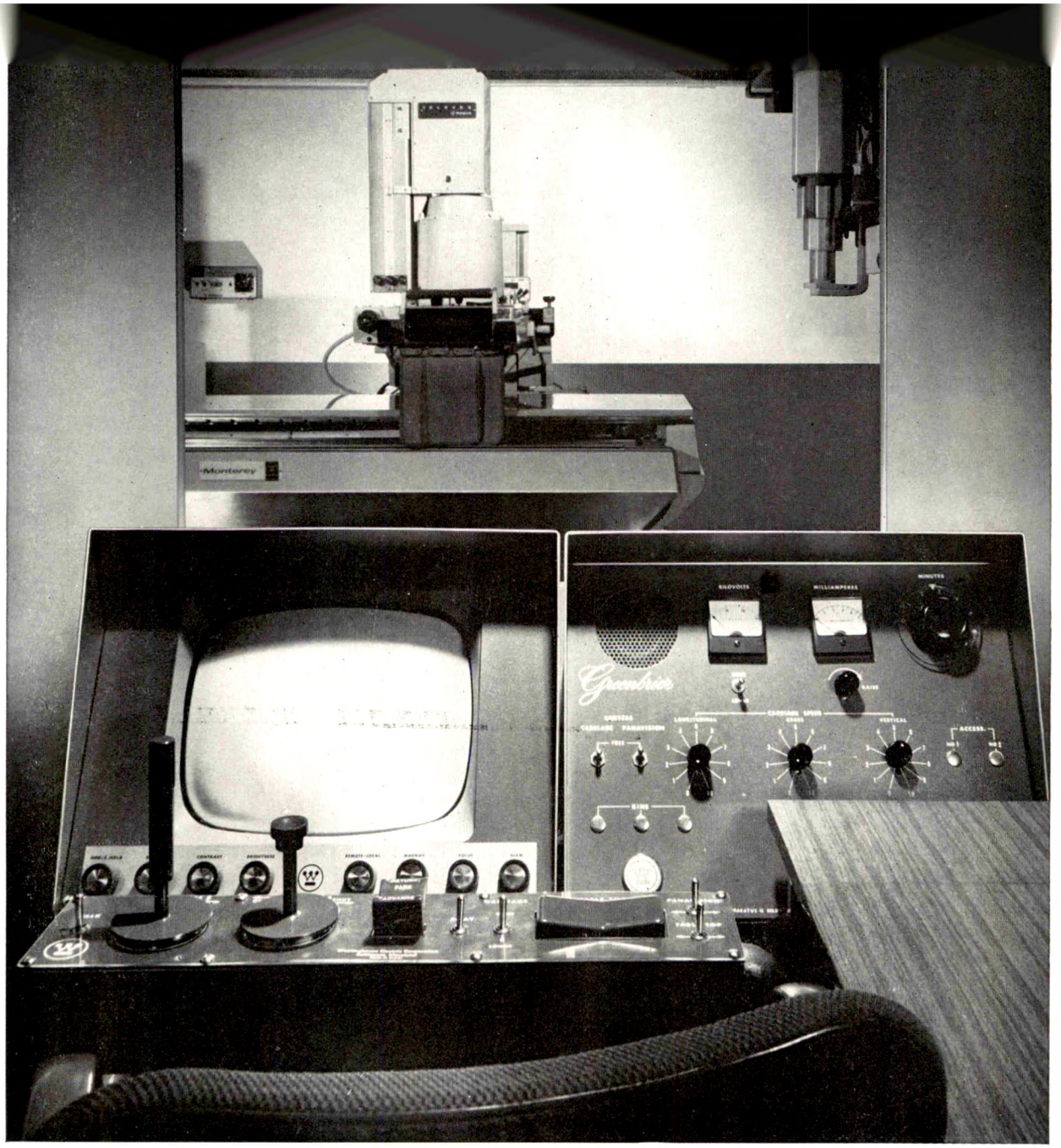
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RECENT DEVELOPMENTS IN ISOTOPE PRODUCTION AND SOURCE FABRICATION*

By PAUL C. AEBERSOLD, PH.D.†
WASHINGTON, D. C.

TREMENDOUS strides have taken place in the past decade in man's capacity to make radioactive atoms. The number of known kinds of man made radioactive atoms is now close to 1,000. Radium 226, *the isotope of radium whose medical use generated this Society*, is now just one of hundreds of useful radioactive species. The total activity of radioactive materials produced by nuclear chain reactions, both controlled and uncontrolled, staggers the imagination. The energies and beam intensities of nuclear particle accelerators have increased a thousandfold and more. Thus, man is now in the fortunate technical position of being able to develop production of any desired radioisotope in sufficient amount and purity to meet all demonstrated needs.

Physicians and medical research workers are already making good use of those isotopes that have become readily available.[1] Of the potentially available radioisotopes, however, only a dozen or so are used routinely in diagnosis and therapy, and fewer than 100 in medical research. Progress in radiation instrumentation, isotope scanning techniques, whole body counting, *in vitro* diagnosis and combined radiation-chemotherapy will assure more extensive uses of presently available radioactive materials. However, for significant advances we must continually seek new isotopic materials and new ways of applying known but little used isotopes.

Steady progress has been made in isotope production toward lower costs, higher specific activities (activity of the desired radioisotope per gram of the total element present), improved radiochemical purity, and greater availability of isotopes having unique half lives and radiation characteristics.

A gross indication of progress in the production, distribution and use of radioisotopes can be obtained from Table 1, *A* and *B*. This table lists the number of shipments and totals of the activity of major reactor-produced radioisotopes distributed for all purposes by Oak Ridge National Laboratory from the beginning of distribution through March 1, 1962. Much smaller

* Presented at the Forty-fourth Annual Meeting of the American Radium Society, New York City, April 2–4, 1962.
† Director, Division of Isotopes Development, U. S. Atomic Energy Commission, Washington, D. C.

TABLE I

DISTRIBUTION OF REACTOR RADIOISOTOPES FROM OAK RIDGE NATIONAL LABORATORY
August 2, 1946–March 1, 1962

Isotope	Shipments	Curies
(A) Items Totaling Over 1,000 Curies		
Cesium 137	1,792	222,533
Cobalt 60	2,755	1,058,869
Gold 198	743	1,019
Hydrogen 3	1,379	150,293
Iodine 131	48,805	7,324
Iridium 192	992	47,187
Krypton 85	608	15,063
Phosphorus 32	31,030	1,962
Promethium 147	509	4,893
Strontium 90	990	100,408
Total	89,603	1,609,551
(B) Items Totaling Less Than 1,000 Curies		
Calcium 45	2,905	36
Calcium 47*	331	0.4
Carbon 14	4,139	156
Chromium 51	1,669	83
Iodine 125**	76	1
Iron 59	2,965	10
Potassium 42	3,311	54
Sodium 24	2,818	22
Strontium 89	1,178	61
Sulfur 35	4,916	183
Xenon 133	25	648
Others (~70 radioisotopes)	45,254	1,824
Total	69,587	3,078
Grand Total	159,190	1,612,629

* Distributed only since October, 1961.
** Distributed only since July, 1960.

quantities of unprocessed radioisotopes have been distributed through the reactor irradiation services provided directly to users by other Atomic Energy Commission laboratories.

Privately owned reactors have also begun to supply certain radioisotopes, notably cobalt 60. Another important addition to the quantities in Table 1, *A* and *B* imports, mainly from Canada and the United Kingdom, of such isotopes as cobalt 60, iodine 131 and carbon 14. Precise figures on these imports are not available, but it is estimated that imports plus private reactor production raise the total activity of all radioisotopes distributed to date in the United States to well over 2,500,000 curies. In addition, three unusually large cobalt 60 government facilities will become operational in 1962: (1) 1,420,000 curies at the Army Quartermaster Radiation Laboratory, Natick, Massachusetts; (2) 600,000 curies at the Brookhaven National Laboratory, Long Island, New York; and (3) 100,000 curies at the Bureau of Mines Laboratory, Albany, Oregon.

PRODUCTION

REACTOR NEUTRON IRRADIATION

Invention of the nuclear reactor made possible widespread applications of radioisotopes. It gave us for the first time the capacity to produce essentially unlimited quantities of neutrons. Neutrons are indeed the magic "touchstone" sought by ancient alchemists. Because they have no nuclear charge, neutrons penetrate readily into any nucleus, thus producing a wide variety of new nuclear species.

Radioisotopes are produced in nuclear reactors by several processes: (1) simple neutron capture, (2) neutron capture followed by decay to the desired species, (3) transmutation, due to capture of a neutron followed by the immediate emission of a proton or in some cases alpha particles or several particles simultaneously, (4) transmutation due to triton (hydrogen 3 nucleus) bombardment resulting from mixture of the target material with lithium 6, and (5) fission of uranium or other reactor fuels.[5,16,17,18] In each case, the production process is characterized by concurrent buildup of the desired product and its exponential decay, as shown by the equation

$$A(t) = P\left[1 - e^{-\frac{0.693}{T}t}\right]$$

where $A(t)$ is the activity produced as a function of exposure time t, $T_{\frac{1}{2}}$ is the half life of the radioisotope produced, and P is the rate of production. P is directly proportional to the neutron flux and the nuclear transformation characteristics of

the target material; *i.e.*, the cross section for the production process of interest as well as for competing reactions. For an infinitely long exposure and a constant amount of target material, a certain maximum activity would be reached where production is equal to radioactive decay. For practical purposes irradiations are seldom conducted for more than three half lifes.

This simple expression for radioisotope production is complicated by several factors: a number of nuclear reactions may be occurring simultaneously, a significant amount of the target may be used up in long irradiations, and the desired product may itself undergo nuclear reactions.

If the radioactive product has a high cross section for neutron capture, it will be "burned-up" in long exposures. Burnup may be undesirable not only because of loss of the valuable material but also because the isotope produced by the sequence of neutron absorptions may itself be radioactive and have undesirable radiation characteristics. In such a case, a brief irradiation in an intense flux is desirable to avoid the production of significant quantities of the unwanted radioactive contaminant. Prompt removal of the desired radioisotope also may be needed to avoid burnup or to minimize secondary reactions leading to radiochemical impurities. This may be achieved by circulating fluid or gas target materials through the reactor in a closed loop—continuous rather than batchwise radioisotope production. The desired isotope may be continuously extracted outside the reactor, avoiding undesirable buildup or burnup problems.

An example of isotope production in which these problems of burnup and radioactive contamination occur is the formation of the low energy photon emitter iodine 125 by reactor irradiation of xenon gas. The target nucleus, xenon 124, which occurs only to 0.096 per cent in the natural isotopic mixture, is activated to xenon 125. The latter decays with an 18 hour half life to iodine 125, which then decays with a 60 day half life. Unfortunately, the product iodine 125 has a substantial neutron absorption cross section for production of 13.3 day iodine 126, which emits a number of high energy beta and gamma rays. Optimum production of iodine 125 thus requires a limited irradiation time to minimize its burnup. In addition, a period of about 3 month's decay is necessary to minimize whatever iodine 126 is formed. At present, the xenon is bombarded in batch irradiations at 100 to 200 lb./in.^{2}. Curie quantities can readily be produced with less than 2 per cent content of iodine 126. The possibility of circulating the target xenon in a closed loop so that the intermediate xenon 125 will decay outside the reactor is being studied as a means of obtaining higher specific activity and purer iodine 125.

Fortunately for the production of most radioisotopes, burnup of the desired product is not a problem. Cobalt 60 is a case in point; long-term irradiation of stable cobalt (monoisotopic cobalt 59) in general leads simply to greater specific activities. Although cobalt 60 itself has a moderate cross section for neutron absorption, thus forming cobalt 61, radiation contamination is avoided because of the short 1.65 hour half life of the latter, which decays to a stable nickel isotope. The quantity of nickel produced is usually so minute that it does not represent a significant impurity nor does it reduce the activity of a given source to a serious extent.

If the target element consists of a mixture of stable isotopes, several concurrent nuclear reactions may go on, leading to a mixture of radioisotopes of the same element that are not separable by chemical means. In some cases, however, the product isotopes differ so greatly in decay rates that a feasibly short storage time will result in material consisting principally of the longer lived radioisotope. In other cases it may be essential to separate the stable isotopes before using them as target material.

One of the most important factors in the production of isotopically and radiochemically pure materials has been the increased availability of higher neutron fluxes. Before

TABLE II

SOME REACTORS USED FOR RADIOISOTOPE PRODUCTION

Reactor	Approximate Maximum Thermal Flux (neutrons/cm.^{2}/sec.)
Oak Ridge Graphite (X-10) Oak Ridge National Laboratory Oak Ridge, Tennessee	1.1×10^{12}
Battelle Research Battelle Memorial Institute Columbus, Ohio	4×10^{13}
Brookhaven Graphite Research (BGRR) Brookhaven National Laboratory Upton, Long Island, New York	2×10^{13}
Argonne Research (CP-5) Argonne National Laboratory Lemont, Illinois	6×10^{13}
Western New York Nuclear Research Center University of Buffalo Buffalo, New York	2×10^{13}
Massachusetts Institute of Technology Cambridge, Massachusetts	3×10^{13}
Union Carbide Nuclear Company Research Tuxedo, New York	3.1×10^{13}
General Electric Materials Testing (GETR) Vallecitos Atomic Laboratory Pleasanton, California	2.4×10^{14}
Oak Ridge Research (ORR) Oak Ridge National Laboratory Oak Ridge, Tennessee	1.1×10^{14}
Materials Testing (MTR) National Reactor Testing Station Idaho Falls, Idaho	5×10^{14}
High Flux Isotope (HFIR) Oak Ridge National Laboratory Oak Ridge, Tennessee (Under construction)	3-to-5×10^{15}

Note: Many other reactors are used to prepare small amounts of radioisotopes for research purposes and occasionally for sale, but are not primary sources of commercial quantities.

the advent of intense neutron fluxes, it was necessary to resort to transmutation, fission, or Szilard-Chalmers reactions with subsequent complicated chemical isolation procedures to obtain radioisotopes of high specific activity. With several reactors available for isotope production with neutron fluxes of 10^{14} neutrons/cm.^{2}/sec. or greater (Table II), satisfactory material can now be obtained in many cases by simple neutron capture reactions. Further increases in flux to the 10^{15} n/cm.^{2}/sec. region as in the new High Flux Isotope Reactor (HFIR) under construction at Oak Ridge will extend this trend.

Scheduled for completion in 1964, the HFIR is intended primarily as a production facility for gram quantities of californium and other transplutonium elements, but it will also have space for production of useful medical isotopes. Its flux of 3-to-5×10^{15} n/cm.^{2}/sec. will be the world's most intense neutron flux. This will permit production of radioisotopes with specific activities over 1,000 times greater than with the original X-10 graphite reactor.

Almost all radioisotope production would be benefited by having higher-flux reactors available. In particular, much higher specific activities of short-lived isotopes could be produced—unless burnup of the desired product is a factor. The short half life makes it practical to go essentially to "saturation," where the rate of production is equal to the rate of decay. Saturation is the theoretical maximum production and in all cases is directly proportional to flux. An example of the advantage of high flux (Table III) is in the production of sodium 24, which has a 15 hour half life and a very low cross section for neutron absorption. The ten-times-higher flux gives material having ten times the activity per gram of starting material.

On the other hand, a high flux is of less advantage when the short lived product has a high cross section for neutron absorption. In this case, maximum production is much below the saturation value. Gold 198 is an example. As shown in Table III, it has a high cross section for burnup of 26,000 barns. Less than twice the activity per gram of starting material can be obtained in this case for a ten-fold increase in flux.

With high fluxes, reactor irradiation could be continued beyond the point of maximum production in order to burn up

TABLE III

EXAMPLES OF EFFECT OF NEUTRON FLUX ON SPECIFIC ACTIVITY

Radio-isotope	Half Life	Target Isotope	Natural Abundance of Target Isotope (per cent)	Activation Cross Section of Target Isotope (barns)	Cross Section of Product Isotope (barns)	Theoretical Specific Activity‡ (curies/gram)	Effect of Flux in Production of the Maximum of Radioisotope/Unit Weight of Starting Target			
							Activity at Maximum		Time to Maximum	
							$\phi = 10^{14}$	$\phi = 10^{15}$	$\phi = 10^{14}$	$\phi = 10^{15}$
Cu^{64}	12.87 hr.	Cu^{63}	69.1	4.51	*	3.8×10^6	80	800	193 hr.	151 hr.
Na^{24}	15 hr.	Na^{23}	100	0.525	*	8.7×10^6	37	370	268 hr.	218 hr.
Ga^{72}	14.2 hr.	Ga^{71}	39.8	5	*	3.1×10^6	45	450	209 hr.	162 hr.
I^{130}	12.5 hr.	I^{129}	100	24	18	1.9×10^6	300	3,000	158 hr.	116 hr.
K^{42}	12.47 hr.	K^{41}	6.91	1.3	*	5.6×10^6	3.6	36	211 hr.	169 hr.
Au^{198}†	2.7 da.	Au^{197}	100	96	(?) 26,000	2.4×10^5	420	810	13.2 da.	2.3 da.
Au^{199}†	2.7 da.	Au^{197}	100	96	*	2.4×10^5	790	7,900	22.4 da.	13.8 da.
Ba^{133}	7.2 yr.	Ba^{132}	0.097	7	*	375	0.054	0.19	19.8 yr.	6.7 yr.
Tl^{204}	4.1 yr.	Tl^{203}	29.5	8	*	429	13.7	55.9	13.2 yr.	4.8 yr.
Ni^{63}	80 yr.	Ni^{62}	3.66	15	*	71	1.79	2.43	43.9 yr.	8.6 yr.
Co^{60}	5.27 yr.	Co^{59}	100	36	6	1,140	368	798	7.5 yr.	1.7 yr.

* Data not available.
† To show effect of extremely high product cross section; 26,000 barns doubtful, but is reported in the literature.
‡ Curies per gram of target material originally present.
ϕ Reactor flux, neutrons/cm.^{2}/sec.

more *target* atoms. This has the effect of increasing the true specific activity (curies of desired isotope per gram of its element). At the same time, if the cross section of the product is comparable to or higher than that of the target, burnup of the product introduces other elements by transmutation reactions. Therefore, to take full advantage of the increase in specific activity through target burnup, it is necessary to chemically separate the desired product element. In the case of cobalt 60, for example, it should be possible by very intense neutron irradiation of cobalt 59, followed by chemical separation of the transmutation product nickel, to closely achieve the theoretical specific activity of 1,140 curies per gram. For short lived isotopes such as sodium 24, however, the theoretical specific activities are so enormous that attaining them would be impractical by this method even if desired.

A significant advantage of high-flux reactors is the possibility of producing high-specific-activity material by (n, γ) reactions that must now be made by neutron transmutation of another element, with subsequent expensive chemical separation. Phosphorus 32, for example, which is made by neutron bombardment of sulfur, could be made directly from a stable phosphorus 31 target. With a 10^{15} neutron/cm.^{2}/sec. flux, activities of more than 100 curies per gram could be obtained by this route at a greatly reduced cost.

Intense neutron fluxes may contribute to better production methods in other ways. Secondary reactions, in which target nuclei absorb two or more neutrons in series, become important and may permit routine production of radioisotopes that cannot now be obtained economically if at all.

In production processes in which a mixture of radioisotopes is obtained, high fluxes offer the possibility of burning up the unwanted contaminants, that is, converting them to materials with a short half life or to a different element so that chemical separation is possible.

Large scale production of radioisotopes in a reactor may present difficulties by affecting the operation of the reactor adversely. Thus, a strongly absorbing target may depress the flux of neutrons in its vicinity by absorbing neutrons that otherwise would continue the chain reaction. Specific activity of the product radioisotope can be increased by irradiating smaller

portions and then assembling them after irradiation. Cobalt metal is bombarded in thin wafers for later assembly in sizable sources for teletherapy. In this way it has been possible, for example, to activate 31 per cent of a cobalt target to cobalt 60, which corresponds to a specific activity of 330 curies/gram.

ENRICHMENT OF TARGET MATERIAL

Targets containing only one isotope of the target element offer great advantage for producing radioisotopes having high specific activity and radiochemical purity. When several stable isotopes of an element exist, isotopic enrichment of the desired target isotope can be performed in electromagnetic separators. As a result, the ratio of activities of a desired radioisotope to unwanted radioisotopes may be raised to almost any desired value. Oak Ridge National Laboratory began its electromagnetic separation program over 15 years ago with the enrichment of two stable isotopes of copper. The program has grown until all the known stable isotopes—more than 250—are now routinely available in enriched form.

Examples of better and less expensive radioisotope preparations produced from enriched isotopes are chromium 51, from enriched chromium 50; iron 59, from enriched iron 58; and calcium 47, from enriched calcium 46. Calcium 47 is particularly interesting because there has long been a need for a gamma emitting isotope of calcium. Calcium 47 is such an isotope but is also an example of a difficult material to prepare without isotopic enrichment of the target. The natural abundance of calcium 46 is only 0.0033 per cent; thus 1 kg. of natural calcium must be put through an electromagnetic separator to collect only 6 mg. of calcium 46. Since the product material still contains some calcium 44, the reactor irradiation produces calcium 47 contaminated with calcium 45. The activity of calcium 47 available on a routine basis has been raised to a Ca^{47}/Ca^{45} ratio of 40:1 (when shipped).

As a result of the use of enriched isotopes, much higher specific activities of the most useful isotopes can be produced in a given reactor (Table IV).

FISSION PRODUCTS

Fission of reactor fuels leads to an intensely radioactive mixture of approximately 200 radioactive species. The half lives of the fission fragments range from microseconds to millions of years. Included are such medically important radioisotopes as iodine 131, strontium 90, cesium 137 and krypton 85. Iodine 131 is currently made at Oak Ridge National Laboratory by neutron fission of highly enriched uranium 235. This is an economical process but not suitable for production by private industry because other fission products are produced and must be handled. Iodine 131 made commercially is produced by the reactor irradiation of tellurium.

The great quantities of radioactive wastes produced when reactor fuel elements are processed to recover unreacted uranium have long been recognized as valuable reservoirs of long lived fission products, such as strontium 90, cesium 137 and cerium 144, for use in medical therapy, isotopic power generators and heat sources.

A milestone in making available very large quantities of fission products, such as cesium 137, was the completion of the Fission Product Development Laboratory at Oak Ridge National Laboratory. This facility makes possible separation and purification of kilocurie to megacurie amounts of the important long lived fission products.

For teletherapy purposes, the advantages of having cesium 137 as free as possible of cesium 134 contaminant are well recognized. Changes in radiation output with a mixed source are significant over a fairly short time since cesium 134 decays with a 2.3 year half life, while cesium 137 decays with a half life of 27 years. Furthermore, the highly penetrating gamma rays of cesium 134 (1.36, 1.17, and 1.04 mev.) compared with the monoenergetic 0.66 mev. gamma rays of cesium 137 present shielding problems. As Beique and Lougheed[4] point out in presenting data on re-

TABLE II

SOME REACTORS USED FOR RADIOISOTOPE PRODUCTION

Reactor	Approximate Maximum Thermal Flux (neutrons/cm.^{2}/sec.)
Oak Ridge Graphite (X-10) Oak Ridge National Laboratory Oak Ridge, Tennessee	1.1×10^{12}
Battelle Research Battelle Memorial Institute Columbus, Ohio	4×10^{13}
Brookhaven Graphite Research (BGRR) Brookhaven National Laboratory Upton, Long Island, New York	2×10^{13}
Argonne Research (CP-5) Argonne National Laboratory Lemont, Illinois	6×10^{13}
Western New York Nuclear Research Center University of Buffalo Buffalo, New York	2×10^{13}
Massachusetts Institute of Technology Cambridge, Massachusetts	3×10^{13}
Union Carbide Nuclear Company Research Tuxedo, New York	3.1×10^{13}
General Electric Materials Testing (GETR) Vallecitos Atomic Laboratory Pleasanton, California	2.4×10^{14}
Oak Ridge Research (ORR) Oak Ridge National Laboratory Oak Ridge, Tennessee	1.1×10^{14}
Materials Testing (MTR) National Reactor Testing Station Idaho Falls, Idaho	5×10^{14}
High Flux Isotope (HFIR) Oak Ridge National Laboratory Oak Ridge, Tennessee (Under construction)	3-to-5×10^{15}

Note: Many other reactors are used to prepare small amounts of radioisotopes for research purposes and occasionally for sale, but are not primary sources of commercial quantities.

the advent of intense neutron fluxes, it was necessary to resort to transmutation, fission, or Szilard-Chalmers reactions with subsequent complicated chemical isolation procedures to obtain radioisotopes of high specific activity. With several reactors available for isotope production with neutron fluxes of 10^{14} neutrons/cm.^{2}/sec. or greater (Table II), satisfactory material can now be obtained in many cases by simple neutron capture reactions. Further increases in flux to the 10^{15} n/cm.^{2}/sec. region as in the new High Flux Isotope Reactor (HFIR) under construction at Oak Ridge will extend this trend.

Scheduled for completion in 1964, the HFIR is intended primarily as a production facility for gram quantities of californium and other transplutonium elements, but it will also have space for production of useful medical isotopes. Its flux of 3-to-5×10^{15} n/cm.^{2}/sec. will be the world's most intense neutron flux. This will permit production of radioisotopes with specific activities over 1,000 times greater than with the original X-10 graphite reactor.

Almost all radioisotope production would be benefited by having higher-flux reactors available. In particular, much higher specific activities of short-lived isotopes could be produced—unless burnup of the desired product is a factor. The short half life makes it practical to go essentially to "saturation," where the rate of production is equal to the rate of decay. Saturation is the theoretical maximum production and in all cases is directly proportional to flux. An example of the advantage of high flux (Table III) is in the production of sodium 24, which has a 15 hour half life and a very low cross section for neutron absorption. The ten-times-higher flux gives material having ten times the activity per gram of starting material.

On the other hand, a high flux is of less advantage when the short lived product has a high cross section for neutron absorption. In this case, maximum production is much below the saturation value. Gold 198 is an example. As shown in Table III, it has a high cross section for burnup of 26,000 barns. Less than twice the activity per gram of starting material can be obtained in this case for a ten-fold increase in flux.

With high fluxes, reactor irradiation could be continued beyond the point of maximum production in order to burn up

the target material; *i.e.*, the cross section for the production process of interest as well as for competing reactions. For an infinitely long exposure and a constant amount of target material, a certain maximum activity would be reached where production is equal to radioactive decay. For practical purposes irradiations are seldom conducted for more than three half lifes.

This simple expression for radioisotope production is complicated by several factors: a number of nuclear reactions may be occurring simultaneously, a significant amount of the target may be used up in long irradiations, and the desired product may itself undergo nuclear reactions.

If the radioactive product has a high cross section for neutron capture, it will be "burned-up" in long exposures. Burnup may be undesirable not only because of loss of the valuable material but also because the isotope produced by the sequence of neutron absorptions may itself be radioactive and have undesirable radiation characteristics. In such a case, a brief irradiation in an intense flux is desirable to avoid the production of significant quantities of the unwanted radioactive contaminant. Prompt removal of the desired radioisotope also may be needed to avoid burnup or to minimize secondary reactions leading to radiochemical impurities. This may be achieved by circulating fluid or gas target materials through the reactor in a closed loop—continuous rather than batchwise radioisotope production. The desired isotope may be continuously extracted outside the reactor, avoiding undesirable buildup or burnup problems.

An example of isotope production in which these problems of burnup and radioactive contamination occur is the formation of the low energy photon emitter iodine 125 by reactor irradiation of xenon gas. The target nucleus, xenon 124, which occurs only to 0.096 per cent in the natural isotopic mixture, is activated to xenon 125. The latter decays with an 18 hour half life to iodine 125, which then decays with a 60 day half life. Unfortunately, the product iodine 125 has a substantial neutron absorption cross section for production of 13.3 day iodine 126, which emits a number of high energy beta and gamma rays. Optimum production of iodine 125 thus requires a limited irradiation time to minimize its burnup. In addition, a period of about 3 month's decay is necessary to minimize whatever iodine 126 is formed. At present, the xenon is bombarded in batch irradiations at 100 to 200 lb./in.^{2}. Curie quantities can readily be produced with less than 2 per cent content of iodine 126. The possibility of circulating the target xenon in a closed loop so that the intermediate xenon 125 will decay outside the reactor is being studied as a means of obtaining higher specific activity and purer iodine 125.

Fortunately for the production of most radioisotopes, burnup of the desired product is not a problem. Cobalt 60 is a case in point; long-term irradiation of stable cobalt (monoisotopic cobalt 59) in general leads simply to greater specific activities. Although cobalt 60 itself has a moderate cross section for neutron absorption, thus forming cobalt 61, radiation contamination is avoided because of the short 1.65 hour half life of the latter, which decays to a stable nickel isotope. The quantity of nickel produced is usually so minute that it does not represent a significant impurity nor does it reduce the activity of a given source to a serious extent.

If the target element consists of a mixture of stable isotopes, several concurrent nuclear reactions may go on, leading to a mixture of radioisotopes of the same element that are not separable by chemical means. In some cases, however, the product isotopes differ so greatly in decay rates that a feasibly short storage time will result in material consisting principally of the longer lived radioisotope. In other cases it may be essential to separate the stable isotopes before using them as target material.

One of the most important factors in the production of isotopically and radiochemically pure materials has been the increased availability of higher neutron fluxes. Before

TABLE I

DISTRIBUTION OF REACTOR RADIOISOTOPES FROM OAK RIDGE NATIONAL LABORATORY
August 2, 1946–March 1, 1962

Isotope	Shipments	Curies
(A) Items Totaling Over 1,000 Curies		
Cesium 137	1,792	222,533
Cobalt 60	2,755	1,058,869
Gold 198	743	1,019
Hydrogen 3	1,379	150,293
Iodine 131	48,805	7,324
Iridium 192	992	47,187
Krypton 85	608	15,063
Phosphorus 32	31,030	1,962
Promethium 147	509	4,893
Strontium 90	990	100,408
Total	89,603	1,609,551
(B) Items Totaling Less Than 1,000 Curies		
Calcium 45	2,905	36
Calcium 47*	331	0.4
Carbon 14	4,139	156
Chromium 51	1,669	83
Iodine 125**	76	1
Iron 59	2,965	10
Potassium 42	3,311	54
Sodium 24	2,818	22
Strontium 89	1,178	61
Sulfur 35	4,916	183
Xenon 133	25	648
Others (~70 radioisotopes)	45,254	1,824
Total	69,587	3,078
Grand Total	159,190	1,612,629

* Distributed only since October, 1961.
** Distributed only since July, 1960.

quantities of unprocessed radioisotopes have been distributed through the reactor irradiation services provided directly to users by other Atomic Energy Commission laboratories.

Privately owned reactors have also begun to supply certain radioisotopes, notably cobalt 60. Another important addition to the quantities in Table 1, *A* and *B* imports, mainly from Canada and the United Kingdom, of such isotopes as cobalt 60, iodine 131 and carbon 14. Precise figures on these imports are not available, but it is estimated that imports plus private reactor production raise the total activity of all radioisotopes distributed to date in the United States to well over 2,500,000 curies. In addition, three unusually large cobalt 60 government facilities will become operational in 1962: (1) 1,420,000 curies at the Army Quartermaster Radiation Laboratory, Natick, Massachusetts; (2) 600,000 curies at the Brookhaven National Laboratory, Long Island, New York; and (3) 100,000 curies at the Bureau of Mines Laboratory, Albany, Oregon.

PRODUCTION

REACTOR NEUTRON IRRADIATION

Invention of the nuclear reactor made possible widespread applications of radioisotopes. It gave us for the first time the capacity to produce essentially unlimited quantities of neutrons. Neutrons are indeed the magic "touchstone" sought by ancient alchemists. Because they have no nuclear charge, neutrons penetrate readily into any nucleus, thus producing a wide variety of new nuclear species.

Radioisotopes are produced in nuclear reactors by several processes: (1) simple neutron capture, (2) neutron capture followed by decay to the desired species, (3) transmutation, due to capture of a neutron followed by the immediate emission of a proton or in some cases alpha particles or several particles simultaneously, (4) transmutation due to triton (hydrogen 3 nucleus) bombardment resulting from mixture of the target material with lithium 6, and (5) fission of uranium or other reactor fuels.[5,16,17,18] In each case, the production process is characterized by concurrent buildup of the desired product and its exponential decay, as shown by the equation

$$A(t) = P\left[1 - e^{-\frac{0.693}{T}t}\right]$$

where $A(t)$ is the activity produced as a function of exposure time t, $T_{\frac{1}{2}}$ is the half life of the radioisotope produced, and P is the rate of production. P is directly proportional to the neutron flux and the nuclear transformation characteristics of

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RECENT DEVELOPMENTS IN ISOTOPE PRODUCTION AND SOURCE FABRICATION*

By PAUL C. AEBERSOLD, PH.D.†
WASHINGTON, D. C.

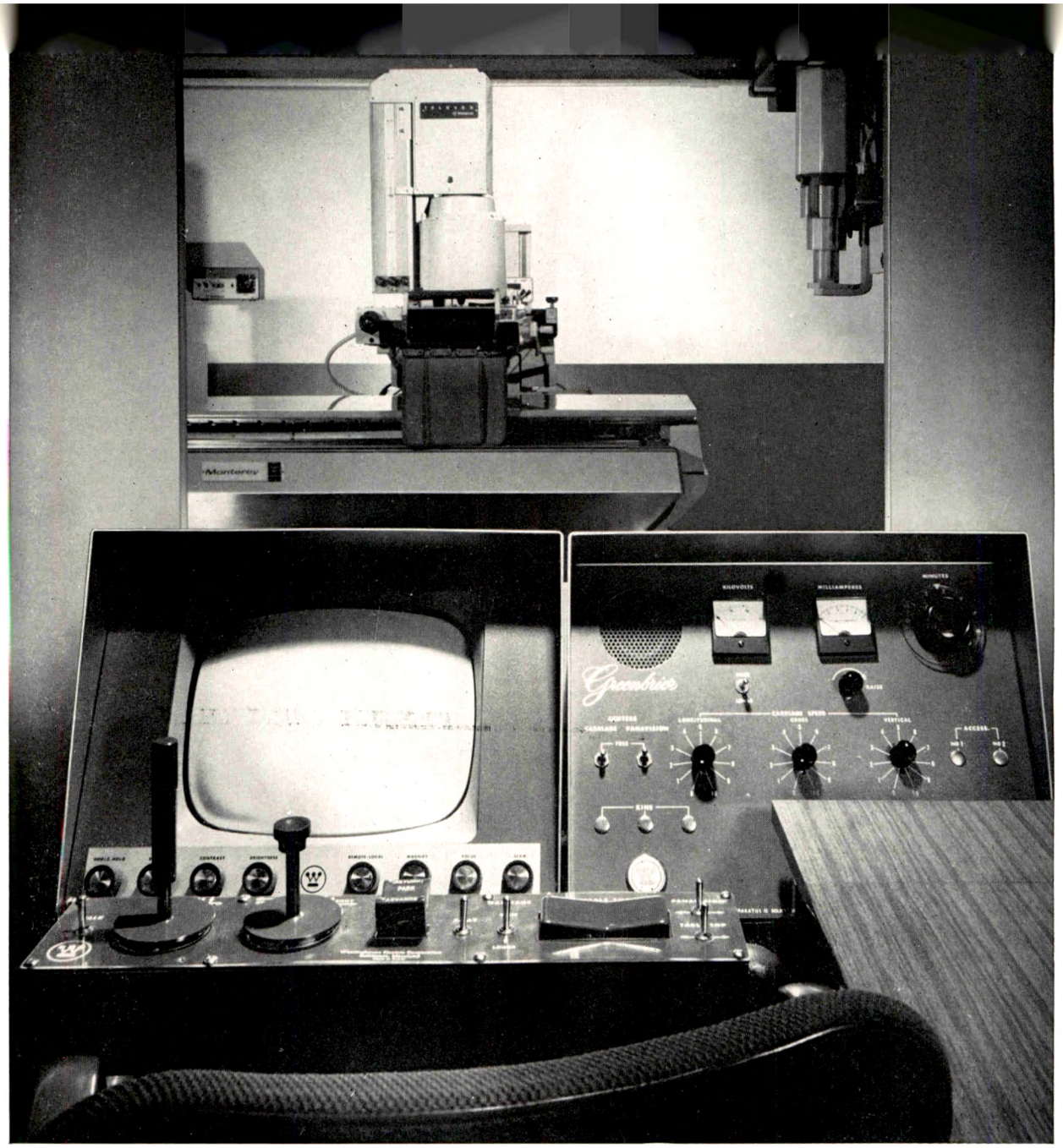
TREMENDOUS strides have taken place in the past decade in man's capacity to make radioactive atoms. The number of known kinds of man made radioactive atoms is now close to 1,000. Radium 226, *the isotope of radium whose medical use generated this Society*, is now just one of hundreds of useful radioactive species. The total activity of radioactive materials produced by nuclear chain reactions, both controlled and uncontrolled, staggers the imagination. The energies and beam intensities of nuclear particle accelerators have increased a thousandfold and more. Thus, man is now in the fortunate technical position of being able to develop production of any desired radioisotope in sufficient amount and purity to meet all demonstrated needs.

Physicians and medical research workers are already making good use of those isotopes that have become readily available.[1] Of the potentially available radioisotopes, however, only a dozen or so are used routinely in diagnosis and therapy, and fewer than 100 in medical research. Progress in radiation instrumentation, isotope scanning techniques, whole body counting, *in vitro* diagnosis and combined radiation-chemotherapy will assure more extensive uses of presently available radioactive materials. However, for significant advances we must continually seek new isotopic materials and new ways of applying known but little used isotopes.

Steady progress has been made in isotope production toward lower costs, higher specific activities (activity of the desired radioisotope per gram of the total element present), improved radiochemical purity, and greater availability of isotopes having unique half lives and radiation characteristics.

A gross indication of progress in the production, distribution and use of radioisotopes can be obtained from Table 1, *A* and *B*. This table lists the number of shipments and totals of the activity of major reactor-produced radioisotopes distributed for all purposes by Oak Ridge National Laboratory from the beginning of distribution through March 1, 1962. Much smaller

* Presented at the Forty-fourth Annual Meeting of the American Radium Society, New York City, April 2–4, 1962.
† Director, Division of Isotopes Development, U. S. Atomic Energy Commission, Washington, D. C.



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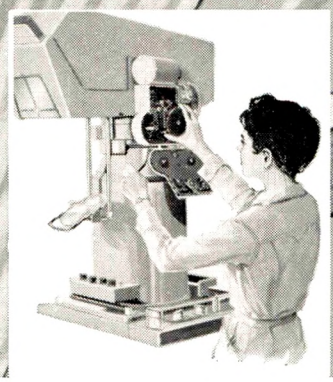
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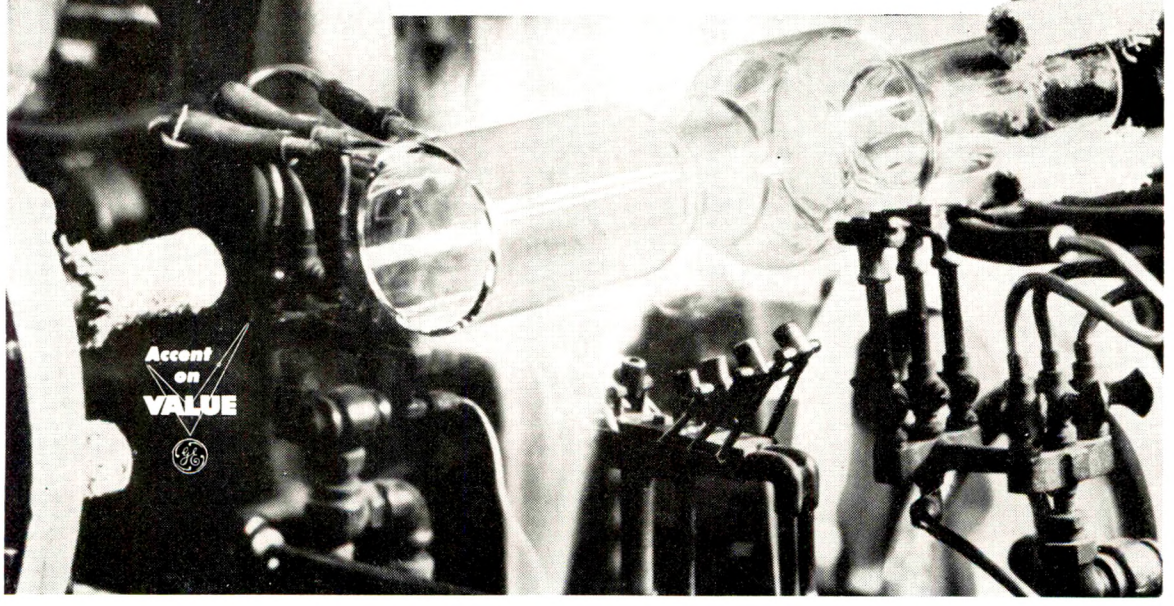
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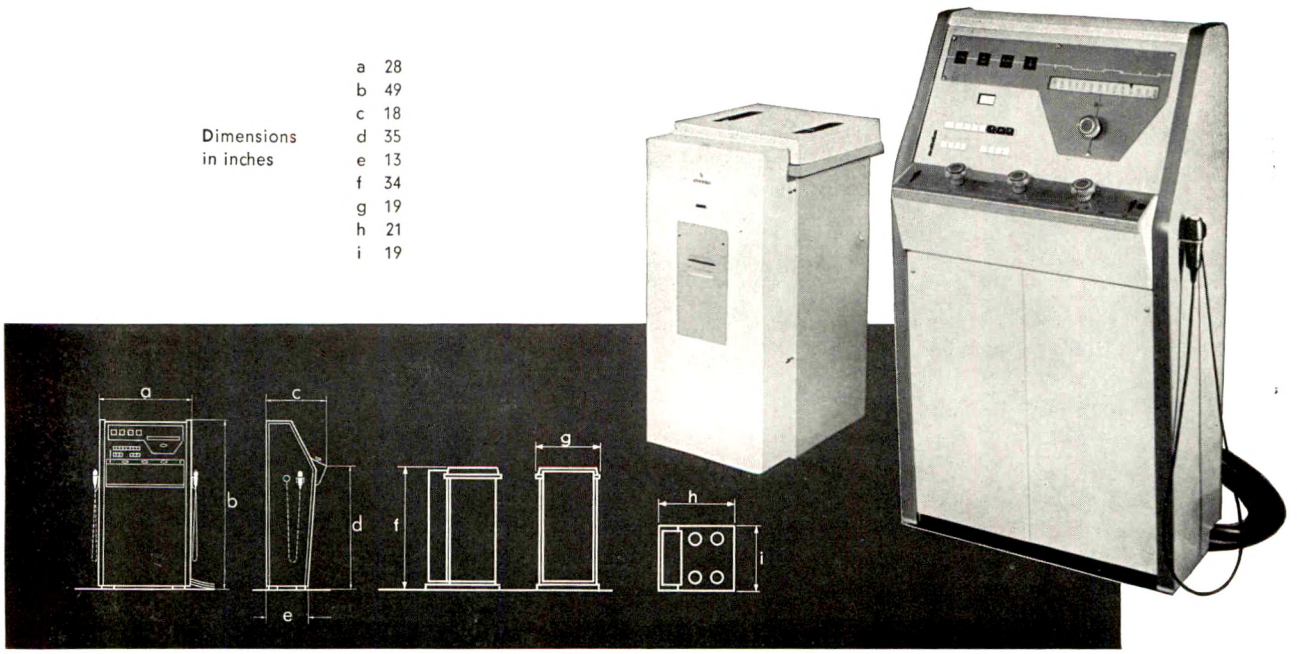
Automatic processing equipment has eliminated practically all darkroom problems. Further simplification and greater efficiency of the radiographic procedure can only be achieved by advanced generator designs such as found in the

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Brookhaven National Laboratory also makes available two short lived isotopes, magnesium 28 and fluorine 18, of particular interest because they are produced by *triton* reactions in a nuclear reactor. Both can be cyclotron produced, but reactor production is advantageous when quantity production and low price are considerations.

Magnesium 28 (21.4 hour half life) is produced by the $Mg^{26}(t,p)Mg^{28}$ reaction using tritons generated by the reaction $Li^{6}(n,t)He^{4}$. The target material is an alloy of 75 per cent lithium 6 and 25 per cent magnesium by weight. At a thermal neutron flux of approximately 1×10^{13}, specific activities ranging from 1 to 2 millicuries of magnesium 28 per gram of stable magnesium are produced by this method.

Fluorine 18 (112 minute half life) is produced in a reactor by the reaction $O^{16}(t,n)F^{18}$ using tritons from the $Li^{6}(n,t)He^{4}$ reaction. It decays by positron emission and has the characteristic annihilation gamma rays associated with it. Although the fluorine 18 half life is short, it is the only isotope of fluorine sufficiently long lived to serve as a tracer. It may also find application in localization work using the annihilation gamma scanning technique.

Iodine 133, with a 21 hour half life, is another short lived isotope now being supplied by Brookhaven National Laboratory. It is a fission product that decays by beta emission and associated gamma rays. Of all the available radioisotopes of iodine, it has the highest ratio of average beta energy to average gamma energy, which makes it useful where maximum local radiation dosage is desired with a minimum of whole body irradiation. Iodine 133 has also found medical application for double-tagging experiments in conjunction with iodine 131.

Isotopes of even shorter life can be produced in the medical laboratory if a source of neutrons is available. Sources of thermal neutrons moderated by paraffin are sold commercially. More recently, accelerator-type neutron generators of convenient size have become available.[6] Some are as small as a few feet in length by 4 inches in diameter. Completely portable, such a device gives up to 10^{8} neutrons per second with an energy of 14 mev. Short lived isotopes that can be produced by these neutron generators include sodium 24 (15 hr.), magnesium 27 (9.5 min.), and aluminum 28 (2.3 min.).

Cyclotrons, too, have been brought within the budget of the small college or research laboratory. One such commercially available cyclotron is only $3\times3\times5$ feet in outside dimensions, yet can provide a 25 microampere beam of 2 mev. protons. Only 2 kilowatts input power is needed. With higher power and minor modifications, proton energies of 8 mev. and beam currents of 1 ma. can be attained. Such low cost machines provide a broad capability for production of short lived isotopes as well as permitting activation analysis and other nuclear techniques.

LOW ENERGY GAMMA AND X RAY EMITTING ISOTOPES

Radioisotopes that emit only one type of energy of radiation permit specific applications without complicating side effects. Thus, isotopes that emit only low energy gamma or x rays have special advantages for diagnosis or therapy, while giving little radiation dose to surrounding healthy tissue and reducing the radiation hazard to operating personnel.

An example of a low energy emitter is palladium 103 which has been used for internal tumor therapy at the Argonne National Laboratory in a number of patients. Some substantial palliation resulted with no serious complications. Palladium 103 emits 20 kev. x rays and has a 17 day half life. In contrast to higher energy gamma emitters, it is easy to work with since a cumbersome lead syringe to protect the surgeon's hands is not necessary. The palladium is injected as palladium black in particles of 100 to 500 microns. Being

highly insoluble and chemically inert, these do not migrate from the tumor site.

Palladium 103 has been obtained by reactor bombardment of palladium metal. Unfortunately, only low specific activity material containing radiation impurities such as neutron-activated iridium is obtained by this method.[10] The precursor palladium 102 has a natural abundance of only 1 per cent. The material can be produced carrier-free in curie quantities by proton bombardment of rhodium, as has been demonstrated with the Oak Ridge National Laboratory 86 inch cyclotron.

Iodine is an excellent example of an element having a wide variety of useful radioisotopes. Of the 20 known radioisotopes, iodine 131 has become most familiar. The advantages of the shorter lived iodine 132 and 133 for certain purposes have already been mentioned. Considerable interest is being shown in iodine 125, a low energy photon emitter, which was overlooked for many years as a potentially valuable medical isotope.[13,22]

Iodine 125 has a number of advantages in comparison with the commonly used iodine 131. The low energy of the 27.3 kev. x rays enhances detector efficiency and contrast, making possible a more accurate scanning technique.[8] At the same time the absence of beta radiation permits comparable studies with only a few per cent of the dose received by the patient if iodine 131 were used. The 60 day half life provides long shelf life and permits long term metabolic studies.

Radiography with low-energy gamma emitters has advanced in practicality with the availability of such isotopes as iodine 125, palladium 103, promethium 147, samarium 145, gadolinium 153, ytterbium 169, and thulium 170 (Table VIII). Highly portable radiography units using various isotopes have demonstrated their capability to produce radiograms of diagnostic quality in locations where x-ray machines are impractical or impossible to use, in operating rooms, homes, disaster areas and remote locations. Besides the advantages of portability and freedom from electrical power requirements, such gamma radiography units can be readily sterilized.[9]

NEW METHODS OF ISOTOPE LABELING

Diagnostic and research applications of radioisotopes require that numerous complex organic compounds be labeled in various positions with radioactive isotopes. The preparation and distribution of labeled compounds and radiopharmaceuticals have for many years been a commerical business. There are dozens of companies bringing out new labeled compounds. The ability to prepare useful radiomaterials often depends on starting with elemental radioisotopes having high specific activities, as produced through Commission development and production activities.

Tritium-labeled materials, while little used except in research, have possibilities for both diagnosis and therapy. The short range beta particles localize radiation effects in regions as small as cell nuclei.

One of the most valuable and commonly used labeling techniques is the Wilzbach self-labeling method, in which organic compounds are simply exposed to large quantities of gaseous tritium.[15,21,23] Modifications include subjecting the system to a silent electrical discharge.[11] While self-labeling has supplied a large number of tritium-labeled compounds, the Wilzbach method has certain disadvantages. Radiolysis produces a mixture of labeled organic com-

TABLE VIII

SOME LOW ENERGY PHOTON EMITTERS SUITABLE FOR RADIOGRAPHY

Isotope	Half Life (da.)	Principal Energies (kev.)
Gadolinium 153	236	42, 70, 97
Iodine 125	60	35
Palladium 103	17	40
Promethium 147	920	*
Samarium 145	360	39, 61
Thulium 170	127	52, 84**
Ytterbium 169	32	110, 130, 198

* Bremsstrahlung from 223 kev. beta particles.
** Plus bremsstrahlung from 970 and 886 kev. beta particles.

pounds which requires difficult and time-consuming separation. The desired labeled compound represents only a small fraction of the initial radioactivity. Furthermore, multicurie quantities of gaseous tritium present a radiation hazard.

A newly discovered labeling technique[24] consists in simply mixing an organic compound with a liquid tritiating reagent—a complex of tritiated phosphoric acid and boron trifluoride—in glass or polyethylene laboratory ware at room temperature.

The reagent is easily made by first combining phosphorus pentoxide with tritiated water to form anhydrous tritiated phosphoric acid, TH_2PO_4, into which is bubbled boron trifluoride gas to form the complex.

In addition to the advantage of convenience, this new technique does not require the use of multicurie amounts of gaseous tritium. High specific activity tracers can be produced using only millicurie quantities of the liquid reagent, although activities up to one curie per gram can also be obtained. The method is faster than any previously available; equivalent labeling can be obtained in 6 hours as compared to more than 1 week by the Wilzbach method. Already demonstrated on a variety of simple aromatic compounds, this tritium-labeling technique is potentially applicable to a major fraction of pharmaceutical and biological compounds.

SOURCE FABRICATION AND SAFETY EVALUATION

Sealed radiation sources, hundreds of which are employed in hospitals in the United States for interstitial or teletherapy use, are continually being improved in regard to safety and utility. Leak proofness has been increased through new methods of encapsulation, while assurance against damage in fires or accidents has been accomplished through improved containment and shielding.

Cobalt 60 for teletherapy is employed in metallic form, usually nickel plated against corrosion, then double encapsulated by welding in stainless steel capsules. Cobalt 60 used in brachytherapy radiation sources may be in the form of metallic cobalt wire, bare or nickel plated, or wire made from a cobalt-nickel alloy (cobium). The cobalt wire may be encapsulated in stainless steel and sealed by Heliarc welding, or in platinum-iridium tubes or needles, which are sealed with a brazed or soldered plug. The cobalt-nickel alloy wires are generally encapsulated in stainless steel tubes or needles sealed with a small screw plug.

Cesium 137 in present teletherapy sources most commonly is used in the form of compacted cesium chloride, double encapsulated in stainless steel or monel. Although cesium chloride is soluble, it does not attack these metals and has the advantage of compactness relative to other cesium compounds.

Beta ray applicators employ strontium 90 which is incorporated in a ceramic or metal matrix, then doubly encapsulated in stainless steel and aluminum so as to leave two thin "windows," one of each metal, for emergence of the beta particles.

In the increasingly unlikely event of containment failure, each radioactive source material itself should be in such a form as to minimize the extent of dispersal and biological absorption—that is, be "inherently" safe. The concept of inherent safety is being achieved by development of highly stable ceramic matrix materials. Proprietary ceramic and fused glass radiation sources are available commercially.

Two new highly stable matrix materials developed under Atomic Energy Commission contracts for isotopic power sources but possessing much wider applicability are (1) strontium titanate and (2) cesium "polyglass."

Strontium titanate is a high density ceramic with a high melting point and extremely low solubility. It provides an excellent way of "locking up" strontium 90 in a useful form until natural decay removes all danger of significant quantities of the radioisotope getting into the environment.

Cesium polyglass is the matrix material used to contain cesium 137 in the isotopic

thermoelectric source which will generate power for an automatic seismograph station to be used on the ocean floor. As a borosilicate glass with a high silicon content, it is unusual among substances containing large concentrations of cesium in being quite insoluble. Its specific activity, however, is not so high as that of other cesium compounds.

Since the number and diversity of uses of sealed radioisotope sources, in new and varied designs, are expected to expand continually, the Commission has undertaken a program to develop standard safety criteria for a wide range of sealed sources.[3,20] Current source compositions, designs and fabrication techniques have been surveyed to evaluate source performance under a wide variety of conditions—thermal, mechanical, chemical, radiation and pneumatic—which might be encountered under both normal and abnormal conditions of use. The resulting data will help to accelerate the safe use of radioisotopes by (1) providing regulatory groups with technical guidance in establishing safe and practical regulatory practices and (2) giving manufacturers definite test goals to meet.

ISOTOPES DEVELOPMENT CENTER

Recognition of the vast potential benefits that will accrue from creative research and development on production and use of radioisotopes has led the Commission to establish an Isotopes Development Center, which is located at its Oak Ridge National Laboratory. Broadened programs of basic and advanced research in isotope technology will be conducted at the Center, which will serve as a focal point for isotope research and development. The Center plans to provide technological data to government agencies, private research groups, industry and educators to assist in expanding beneficial radioisotope applications.

The Center will embrace a complex of radioisotope facilities. It will incorporate the Fission Product Development Laboratory, which develops new methods of separating, purifying and fabricating massive quantities of fission products. Chemical operations on highly concentrated fission products are carried out in shielded cell blocks containing process equipment designed for unattended control of various unit operations such as solvent extraction, evaporation and precipitation. A number of cell blocks are equipped with mechanical manipulators designed for work in intense radiation fields.

More general in purpose will be the new Radioisotopes Development Laboratory. This is located in a reinforced concrete and steel two-story structure, with a gross floor area of about 12,000 square feet. The building will contain four hot cells, a cell-operating area, laboratories, offices, change rooms, storage and utility areas and a three-level chemical engineering area. The laboratory will undertake to advance the development of new processes to improve the availability, purity and diversity of many usable isotopes for research, industrial and medical applications.

Other facilities available to the Isotope Center include stable isotope separators, radioisotope production accelerators, and the Oak Ridge National Laboratory reactors, providing the Center with one of the world's most comprehensive array of research and development laboratories, together with a broad reservoir of technical and scientific ability for furthering isotope progress.

CONCLUSION

Radioisotopes have already made important contributions to basic research vital to nearly all areas of medical progress, to the development of unique diagnostic methods used on millions of patients, and through therapy to the useful prolongation of hundreds of thousands of lives. Nevertheless, opportunities are still expanding. With the increased incentives created by advancing medical needs, progress will be accelerated in the production of isotopes and labeled materials. Concurrently, the almost unlimited possibilities for unique isotopic materials will stimulate creative

thought toward developing new and wider usage.

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Washington, D. C.

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A DOSE DESCRIPTION SYSTEM FOR INTERSTITIAL RADIATION THERAPY*

SEED IMPLANTS

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THE ultimate objectives of physical treatment planning are: (a) to provide a complete specification of the distribution of absorbed dose produced in a given region of an irradiated patient, and (b) to determine the arrangement of the internal radiation sources, or orientation of the externally applied radiation beam, such that the optimum dose distribution is achieved. The dose specification should be in three dimensions, and should ideally also take into consideration the inhomogeneous composition of the body to the extent that this is known. Further, in order that alternative irradiation plans may be considered before treatment must start, this comprehensive dose analysis should be available in a reasonably short period of time. Families of plotted isodose contours in planes throughout the regions in question present the dose data in the most usable form. The application of rapid data-processing computer systems now makes this possible.

The availability of experimentally determined isodose distributions in water for external beams of radiation, together with the relatively limited number of such parameters as distance from the tumor and directions of approach employed, has made it more convenient initially to apply the computing machine approach to external radiation therapy. For the past 7 years all telecobalt radiation therapy cases and many of the other more complicated multiple field combinations of external radiation beams at Memorial Hospital have been planned with the aid of automatic computing methods. For example, the complete isodose distributions for telecobalt rotation (simulated by 12 fields with axes 30 degrees apart) are routinely obtained in about 15 minutes after the patient's contours, the location of the lesion, and the desired field size at the lesion have been established.

Such analysis is more complicated for internally located radiation sources for at least 2 reasons: (a) the location and number of individual internal sources are usually far more varied than the arrangement of external fields and (b) the determination of the actual dose distribution produced by a large number of sources in an absorbing medium is experimentally difficult and has been carried out for only a few simple geometries.

The application of computing-system methods to the problem of implanted sources has made it possible to calculate in a reasonably short period of time the total three-dimensional distribution of dose produced by sources placed in any complex geometric arrangement and to include the effects of attenuation and scattering due to absorption of the radiation by the medium. Although the advantages of this approach are most apparent when applied to individual cases, this approach has also made it possible to obtain the complete dose distributions produced by a large number of complex seed implants which can serve as models.

In this report the use of rapid data-processing techniques for treatment planning with particular application to a large variety of radioactive seed implant arrays, specifically for radium gamma rays, is de-

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scribed. The emphasis here is on the dose distribution produced by any arrangement of sources. This system can be applied to the arrangements prescribed by either the Paterson-Parker or Quimby systems. Later reports will present similar analyses for other radioactive isotopes, as well as for needle and tube arrays. Seed implants are particularly pertinent since their dose distributions tend to be extensive and extremely nonhomogeneous. It is not ordinarily convenient or feasible to implant seeds according to the Paterson-Parker rules designed to attain a homogeneous dose.

SUMMARY OF ESTABLISHED IMPLANT DOSIMETRY SYSTEMS

Two systems of implant dosimetry are established in use: the Paterson-Parker system, and the Quimby system. Both were developed after many years of investigation and experience with implants of radium and radon. These systems are well known and only a few salient features of each pertinent to seed implants will be briefly reviewed here.

The Paterson-Parker system[2,12–15] was developed to achieve a uniform dose distribution in planes intermediate to the implanted planes. The system specified in detail a nonuniform distribution of radioactive sources in order to achieve uniformity of dose to within ±10 per cent of the stated dose in the dose planes 0.5 cm. from the implanted planes. In the case of planar implants, therefore, the absolute minimum dose is 10 per cent less than the stated dose. In the case of cylindrical volume implants, in order to be consistent, Parker[12] (page 331) defined the minimum dose of the volume implant as 10 per cent above the absolute minimum dose to be found in the volume. The tables are given in terms of the milligram-hours necessary to produce 1,000 r for the stated dose of a plane implant or for the minimum dose of a volume implant (planar or cylindrical). No allowance was made for attenuation by absorption or build-up due to scatter. Shalek *et al.*[19] have computed a volume implant table for regularly spaced seeds specified in terms of a minimum dose compatible with the Paterson-Parker system.

The Quimby system[16–18] was developed for those situations where the distribution of radioactive sources is approximately uniform. It is often more convenient to approximate a uniform distribution of sources than the specific nonuniform source distribution prescribed by the Paterson-Parker system. Further, there may be some clinical preference[8] for a higher dose in the central region of a lesion. The dose distribution is consequently less uniform than in the Paterson-Parker system. For planar implants, the Quimby specification is in terms of the maximum dose for various distances from the implant plane; specification for volume implants is in terms of the absolute minimum dose which should be somewhere on the periphery. As in the Paterson-Parker system, the emission constant of radium (0.5 mm. Pt filtration) was used as 8.4 r/mc-hr. at 1 cm.

An IBM computer has been applied by Shalek and Stovall[20] for the computation of the dose at points on a 1 mm. grid around radium needle implants. From these automatically computed data, isodose contours were subsequently drawn manually. A later modification permits the printing of isodose patterns automatically by an IBM 717 printer;[22] the clinical evaluation of 100 past and current cases so calculated has been reported.[4] The development of a computer dose calculation system including a plotter and plotter program such that the actual isodose contours are plotted graphically by the computer system has been described by the authors.[21] This method is sufficiently fast that its results have been used to modify interstitial implants before and during treatment at Memorial Hospital.

Although calculations of the dose distribution produced by a postulated distribution of seeds (or other sources) can be made before implantation, roentgenographic localization and immediate calculation of the

actual dose contours are essential. Mutually perpendicular roentgenograms (anteroposterior and lateral views) are made and analyzed as described by Meredith and Stephenson[10] and by Farr[8]. Analysis of the roentgenograms yields the size and shape of the implanted volume and indicates the uniformity (or lack of it) in the distribution of sources. Localization of individual seeds is possible, but not usually practicable. The use of the after-loading technique,[7] where feasible, can facilitate prior evaluation of dose distributions.

ABSORPTION CORRECTIONS

Previous calculations of dose distributions for implants have not included absorption effects of the tissue and have assumed the dose rates at various distances from a source in air to be applicable in the tissue. Absorption in the tissue modified the dose by attenuation and scattering of the gamma rays. The over-all effect for radium gamma rays is a decrease in dose in tissue compared to that in air with increasing distance from the source. For small distances, less than 5 cm., the correction for a single source is about 10 per cent, but for multiple sources within a 5 cm. radium sphere the correction at any internal point will be less. For larger implants the correction is not negligible. Also, for any dose external to the implant the correction is not negligible, regardless of implant size. The dose external to the implant is needed in many instances where evaluation of the possible dose to other specific organs is needed, particularly in the blood forming regions.

The ratio of the exposure dose in water and in air as a function of distance from radium sources has been studied experimentally by several investigators, including Wootton *et al.*,[26] Ter-Pogossian *et al.*,[23] and Van Dilla and Hine,[25] with comparable results. Wootton *et al.* used both an air-wall ionization chamber and an anthracene crystal with consistent results and their ionization data are shown in Figure 1. Extension of their data to distances beyond

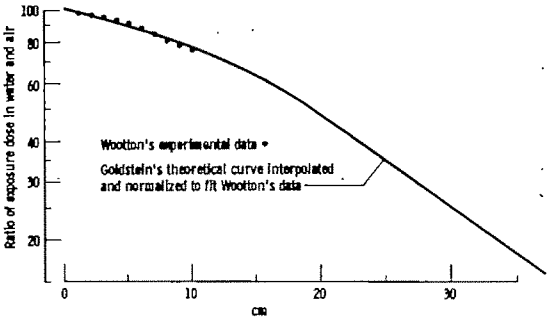


FIG. 1. Ratio of exposure dose produced in water and in air by a point source of radium filtered with 0.5 mm. platinum. Experimental data[26] have been extended by a theoretic calculation.[5]

10 cm. is possible with the aid of a theoretic investigation of gamma-ray penetration by Goldstein and Wilkins.[5] These data were used in an analysis by Hale[6] of the amount of absorption-scatter correction necessary for various isotopes at distances close to the source. Goldstein and Wilkins[5] solved the Boltzman transport equation by the moment method to describe the penetration of different media by gamma rays of various energies. Their results yield values of the effect (Br) of build-up due to scatter for distances (r) greater than one mean free path and were employed in the following manner. The principal gamma rays of radium of energy E_i were weighted by their frequencies to obtain their relative intensity I_i, and the relative exposure dose in water and in air was calculated according to the relation:

$$\frac{\text{Dose in water}}{\text{Dose in air}} = \frac{\sum^{i} I_i \times e^{-\mu_i r} \times Br(E_i, r) \times \mu_{ai}}{\sum^{i} I_i \times \mu_{ai}}$$

where μ_i is the total attenuation coefficient in water for gamma rays of energy E_i, and μ_{ai} is the real fraction of the absorption coefficient in air for gamma rays of energy E_i. This relation was computed for the radium gamma rays and normalized to the experimental data of Wootton *et al.* by an additional exponential factor. The ratios

thus determined were then entered in the computer memory as described below.

COMPUTER PROGRAM

The dose rate at any point with coordinates (X_p, Y_p, Z_p) due to n seeds located at (X_i, Y_i, Z_i) was calculated according to the relation:

$$\text{Dose rate } (X_p, Y_p, Z_p) = I_\gamma \sum_{i=1}^{n} \mathcal{Q}_i \frac{F(r_i)}{r_i^2}, \quad (2)$$

where

$$r_i^2 = (X_p - X_i)^2 + (Y_p - Y_i)^2 + (Z_p - Z_i)^2,$$

$\mathcal{Q}_i$ is the source strength in millicuries,
I_γ is the emission constant, taken as 8.25 r/mc-hr. at 1 cm. for radon,
$F(r_i)$ is the absorption correction as plotted in Figure 1.

Computations of isodose points for the seed configurations studied were carried out on both an IBM 7090 digital computer and a Bendix G-15D digital computer. The program was written in FORTRAN for the 7090, a programming system which makes it possible to communicate with a digital computer in a language similar to algebra. This FORTRAN program is taken by the 7090 and converted into a program consisting of 7090 machine language instructions (the *object* program). This method of programming has two advantages: the FORTRAN language is much simpler to learn and use than machine language thus cutting down programming effort and time; and there are many different computers in use that will accept a FORTRAN program and convert it into their own machine languages. Intercom was used for the Bendix G-15D. Preliminary studies[11] were carried out on the IBM equipment used for telecobalt rotation[24] isodose distributions.

The program will accommodate any equally spaced array of seeds in the shape of a rectangular parallelopiped. The dose at a point in $X\ Y\ Z$ space was calculated by computing the dose from each individual seed (using the inverse square law and the water-air ratio correction) and summing over the entire array. Provision was made to eliminate selected seeds in order to calculate missing seed configurations.

Input to the machine consisted of the following: X, Y, and Z dimensions of the seed array; water-air ratio table; a list of missing seeds, if any; case number for missing seed configurations; and a control constant which signified a type of symmetry that the seed array might possess (to economize on machine calculations). Depending on whether the number of seeds in the Z direction was odd or even, the initial plane was designated as either $z_0 = 0.5$ cm. or $z_0 = 0$ cm. (Figure 3). A square grid of dose values was calculated in this initial plane at 0.5 cm. intervals extending at least 4.5 cm. beyond the periphery of the seed array. This dose grid was scanned for the maximum dose, which served as the "reference maximum dose" for the entire array. Using this "reference maximum dose" as the 100 per cent dose value, the grid was converted into percentages. The dose grid was scanned again along all lines with y = constant, and when two consecutive points bracketed a desired percentage dose (5,10,20,30 . . . 90), the X value for that dose was linearly interpolated for and stored. The machine then entered a plotting routine and output occurred on magnetic tape. This process (calculating a grid, converting to percentages, interpolation, storage and output) was repeated at $z = z_0 + 1.0$, $z_0 + 2.0$, . . . , using the maximum dose found at $z = z_0$, until a distance of at least 4.5 cm. from the top of the array was reached.

The magnetic tape output was then fed into a Stromberg-Carlson 4020 microfilm printer which, by means of a *charactron* tube, photographed the output (in the form of plots) on 35 mm. film. This film was developed and the individual plots put on aperture cards. The finished plots are conveniently printed on a *Xerox* machine.

Organization of the computer program is illustrated in Figures 2*A* and 2*B*, the basic simplified flow charts, showing the over-all program organization and that portion in which the dose is calculated in a given

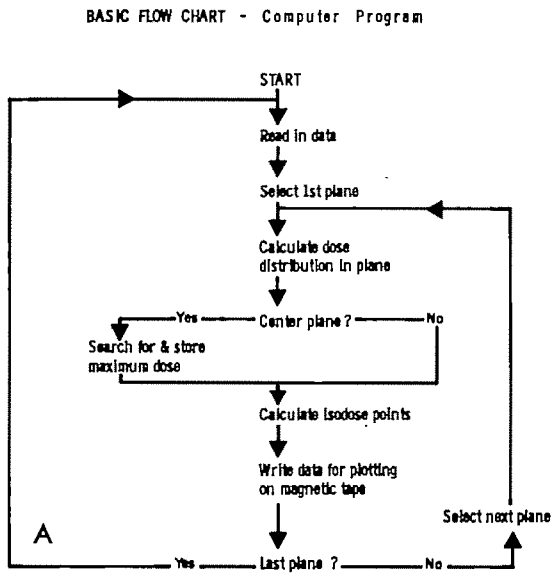


FIG. 2. (*A*) Basic Flow Chart—Computer Program. This chart illustrates the over-all organization of the computer program, the sequence in which the various steps are executed and the major decisions made by the computer. Beginning at "start," this procedure calculates isodose curves in three dimensions for as many implants as desired, and stores the isodose curves on magnetic tape for later automatic plotting.

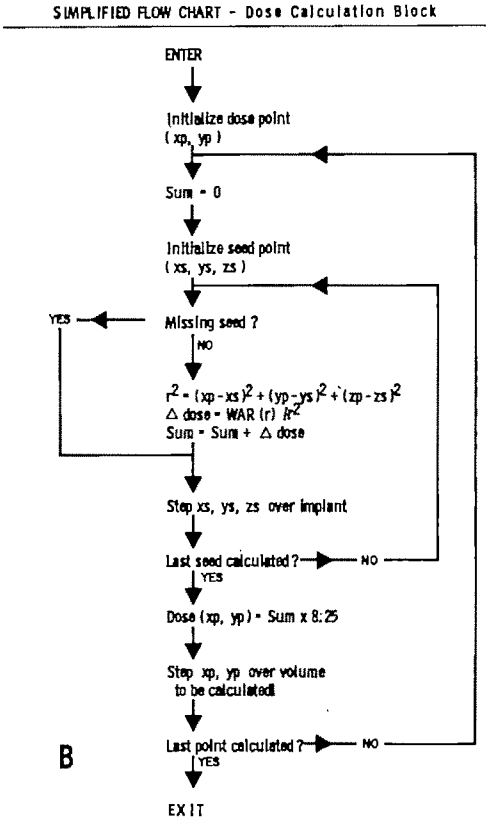


FIG. 2. (*B*) Simplified Flow Chart—Dose Calculation Block. This flow chart shows in greater detail the operations performed in the "calculate dose distribution" block of *A*. The procedure illustrated in this chart calculates the dose from all seeds in a given implant to all points (x_p, y_p) in a given plane z_p.

plane. The flow charts shown are of necessity greatly simplified since the actual flow charts used covered about two dozen pages. Simplification has been achieved by omitting most of the minor but essential logical decisions such as determining whether there were an even or odd number of seeds on a side.

Separate data cards were prepared for each implant to be calculated. Both data and programs were copied from punched cards to magnetic tape prior to entry into the IBM 7090 computer. As shown in Figure 2*A*, calculation commenced by reading in the data for a particular implant. The isodose curves were calculated plane by plane and stored on magnetic tape for later plotting. After the last plane was completed, more data were read in until the last implant was calculated, following which an automatic transfer to the next job took place.

Details of the dose calculation block are shown in Figure 2*B*. Since the calculations are carried out in an X, Y plane, the Z value is transmitted from the main program and does not vary during the calculation in one plane. Figure 2*B* is an enlargement of the block in Figure 2*A* labelled "calculate dose distribution in plane." Calculations and plots of centerline dose were carried out on the Bendix G15-D computer facility at Memorial Hospital.

SEED ARRAYS AND DEFINITIONS OF TERMS

Calculations were carried out for a large variety of seed implants in the shape of planes, cubes, and oblongs. Plane implants ran from 2 to 8 seeds on a side, cubic im-

plants from 2 to 8 seeds on an edge, and oblong implants in a 2:1 ratio from 2×2×4 successively to 5×5×10, and in a 3:1 ratio from 2×2×6 to 5×5×15, all numbers indicating seeds on an edge. Furthermore, typical implants were repeated with various seeds missing to observe this effect on internal isodose contours. In all of the above cases, all of the seeds were located on rectangular lattices 1 cm. apart, as shown in Figure 3. Data with other spacings are being studied and will be reported subsequently.

The dose distributions were determined in intermediate planes, hereafter referred to as "isodose planes." These planes were 1 cm. apart and extended 5 cm. beyond the peripheral edges of the implants. As indicated in Figure 3, isodose planes were calculated up to 5 cm. above and below the seed arrays. In any regular array of sources, 3 sets of mutually orthogonal isodose planes can be constructed. In all cases the dose distribution results in these sets are redundant and are usually so similar that only one set of isodose planes is required and can be selected on the basis of convenience.

The term "reference maximum dose" was applied to the highest dose found in any of a set of isodose planes. In addition to recording its absolute value in r on the basis of an exposure of 1 milligram-hour for each seed in the array, the computer assigned it a relative value of 100 per cent. Locations of the 90 per cent, 80 per cent, . . . 10 per cent, and 5 per cent dose points were then found by the computer and noted, as shown in Figures 4–12.

The term "minimum peripheral dose" was applied to the lowest dose found at the intersection of the periphery of each seed array with the isodose planes. The term "centerline" was applied to a line included in that isodose plane (or planes) containing the reference maximum, and passing through the reference maximum, parallel to an edge of the implant. In the case of a cube or oblong, there are three mutually orthogonal centerlines. The term "centerline peripheral dose" was applied to the value of the dose at the intersection of the centerline and the periphery of the implant.

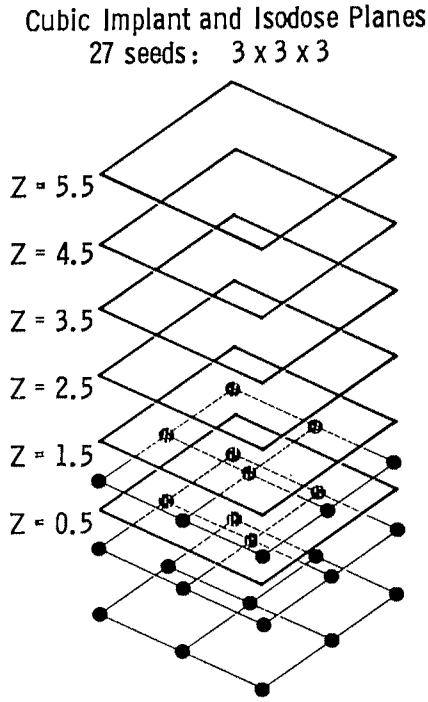


FIG. 3. Typical geometry for volume implant showing location of seeds and dose planes.

In this work, tabulated results have been stated in terms of the number of milligram-hours to produce 1,000 rads in water at the location of the minimum peripheral dose, centerline peripheral dose (where applicable), and reference maximum dose. The factor 0.965 rads in water per roentgen[9] has been employed and must be kept in mind in comparisons with other tables.

RESULTS

DATA PRESENTATION

As noted above, the data are presented by the computer on the face of a *Charactron* tube and microfilmed. Figures 4–12 are prints from the microfilm and show the unmodified computer output. In these figures the digits identifying the isodose points should be multiplied by 10 to give percentages, except that 0 indicates 5 per cent. The absolute value of the reference maximum dose rate in roentgens/milli-

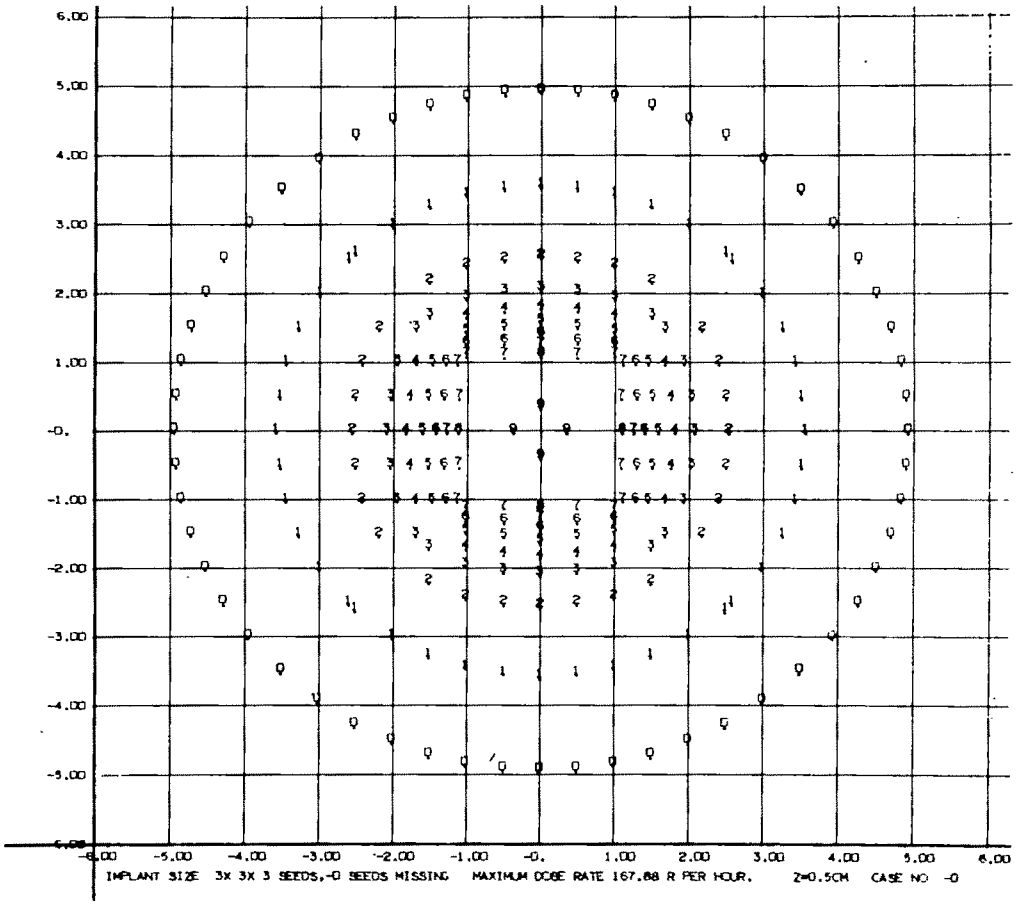


FIG. 4. Computer Output—Isodose Points for 3×3×3 seed implant, $Z=0.5$ cm. (1 cm. grid in this and succeeding figures).

gram-hour/seed is printed by the computer in the legend of each isodose plane, as well as the implant identification, number of missing seeds (if any), and the vertical (Z axis) location of the plane. Figures 4–8 show the data for a 3×3×3 seed cube (27 seeds total). Figure 9 shows a plane 0.5 cm. from a 3×3 seed plane implant with a missing central seed, and Figure 10 shows the central plane for a 5×5×5 seed implant with 25 missing central seeds. Figure 12 shows a central plane for a 6×6 seed plane implant.

The direct computer output as illustrated in Figures 4–12 is not adequate for routine clinical use, and must be replotted for best visualization of the dose distribution. Figures 13–23 show typical final isodose plots. Figures 13–20 are the complete isodose sets for a 5×5×5 seed implant. Of particular interest is a comparison of Figures 13 and 21, showing the central plane dose distribution for a 5×5×5 seed implant without missing seeds (Fig. 13) and with 25 missing central seeds (Fig. 21). Figure 22 illustrates the effect of elongation, and Figure 23 shows the ($Z=0.5$ cm.) plane for a 5×5 seed plane implant.

ANALYSIS

The analysis of such data for the bulk of the configurations studied is shown in Figures 24–31 and in Tables I and II. The variation of absorbed dose in water along the centerline of the cubic implants is shown in Figure 24 as a function of distance from the center out to 20 cm. The periphery of each implant is indicated with an arrow. The lack of homogeneity in dose is pre-

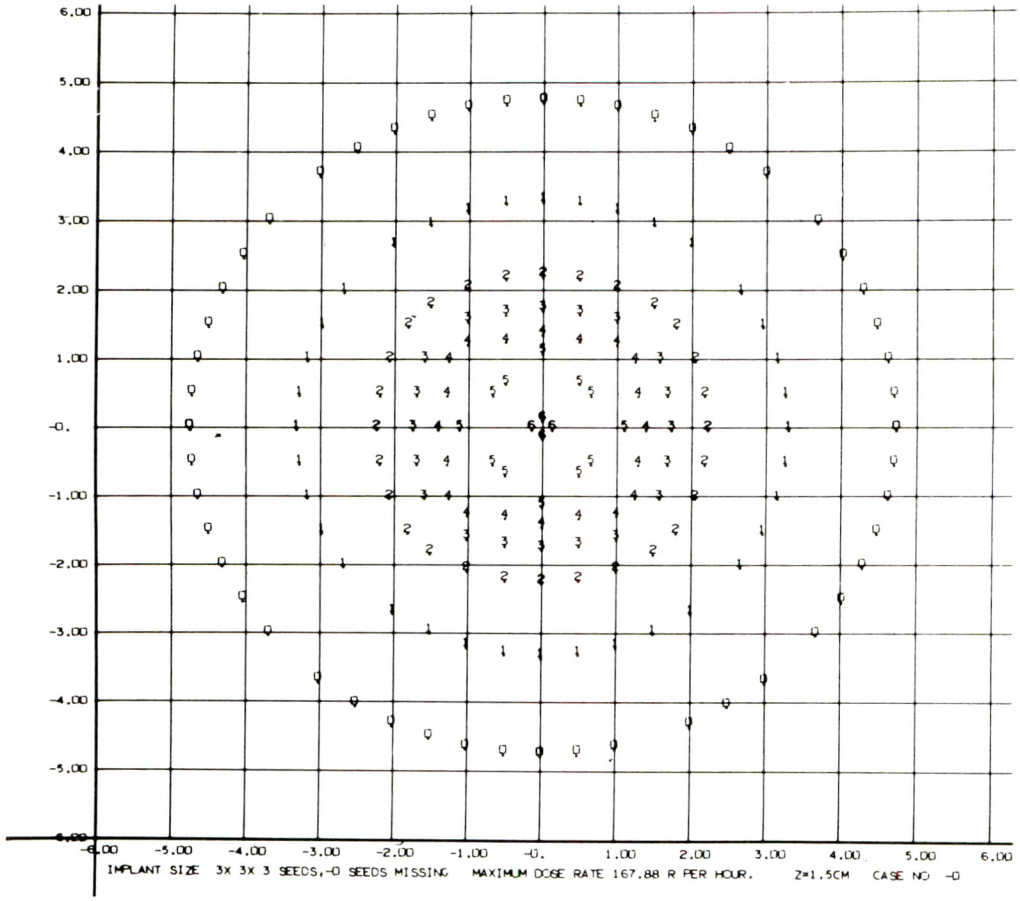


FIG. 5. Computer Output—Isodose Points for $3\times3\times3$ seed implant, $Z=1.5$ cm.

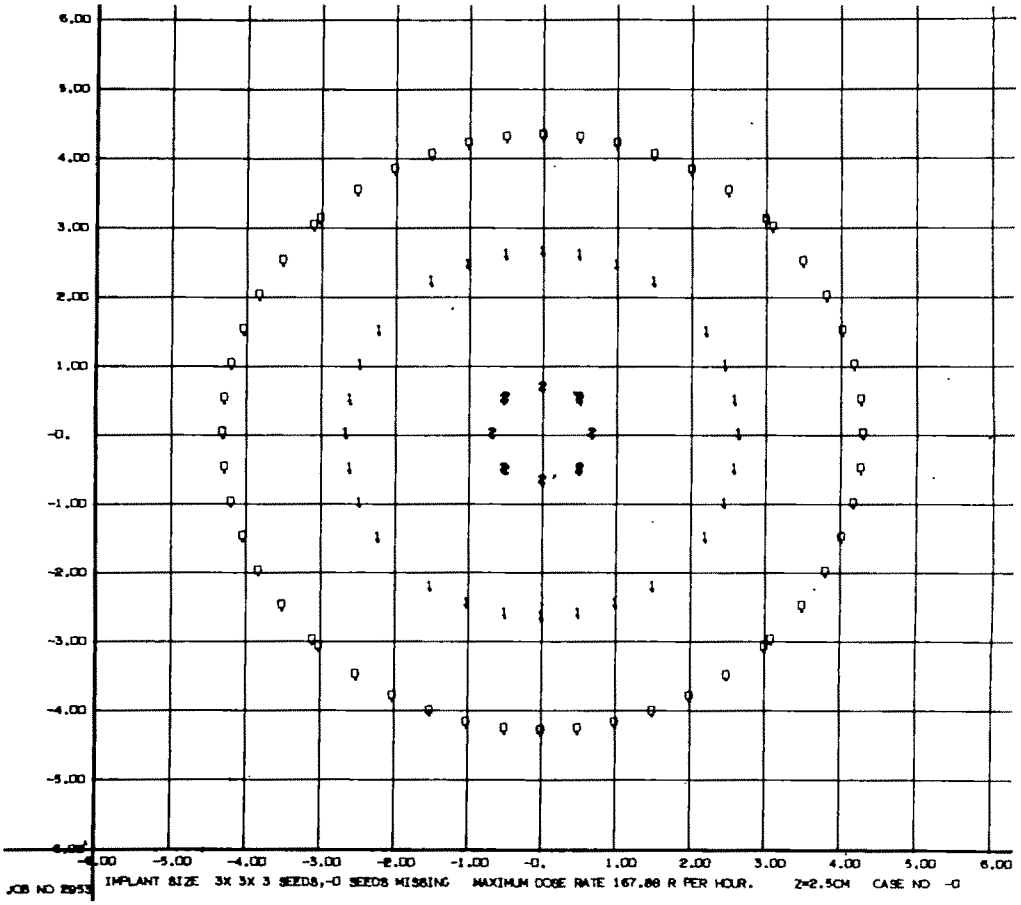
cisely characterized in this dose "profile" through each implant. Figures 25 and 26 show the variation of the centerline dose along the long and short axes, respectively, of oblong implants. Figures 27*A* and 27*B* show the centerline dose "profiles" for planar implants parallel to the implant plane, and perpendicular to the implant plane through the reference maximum dose, respectively.

Figure 28 shows a comparison of the variation of centerline dose for a $5\times5\times5$ seed cubic implant with and without the absorption correction for attenuation and scatter build-up. The correction becomes increasingly important with the distance from the center, amounting to over 20 per cent at 10 cm. from the center.

In Figure 29 the variation is shown as a function of the number of implanted seeds, assuming an exposure of 1 milligram-hour per seed.

Aside from the isodose contours, the most pertinent single criterion is the minimum peripheral dose and this is plotted in Figure 30 for the indicated implants as a function of the number of seeds and in Figure 31 as a function of the implanted volume. It is plotted in terms of the number of milligram-hours necessary to produce 1,000 rads. The corresponding centerline peripheral dose is also plotted for the purpose of comparison on these same graphs.

The isodose contours give the clinician the most complete physical information possible which can be considered directly with respect to the anatomy and the desired distribution of the dose. However, the preceding figures and Tables I and II present


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JOB NO 2953 IMPLANT SIZE 3X 3X 3 SEEDS,-0 SEEDS MISSING MAXIMUM DOSE RATE 167.88 R PER HOUR. Z=2.5CM CASE NO -0

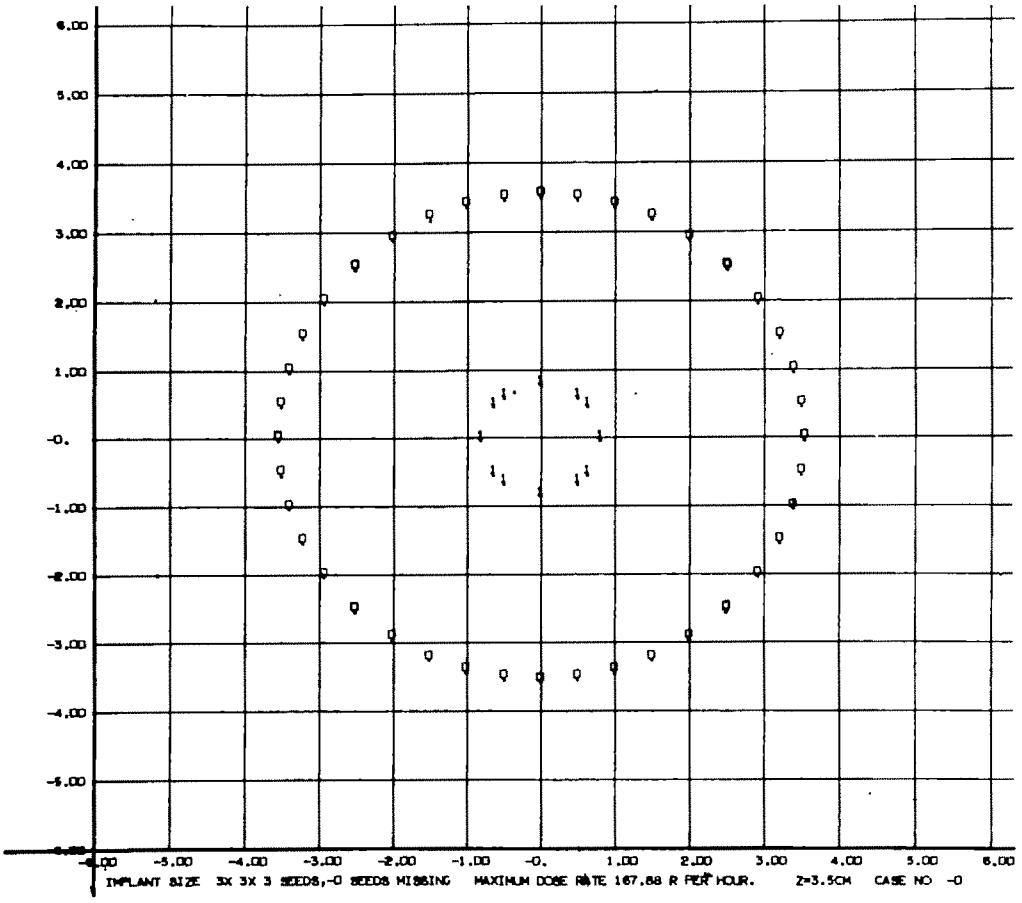

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IMPLANT SIZE 3X 3X 3 SEEDS,-0 SEEDS MISSING MAXIMUM DOSE RATE 167.88 R PER HOUR. Z=3.5CM CASE NO -0

FIG. 6. Computer Output—Isodose Points for $3\times3\times3$ seed implant, $Z=2.5$ cm.

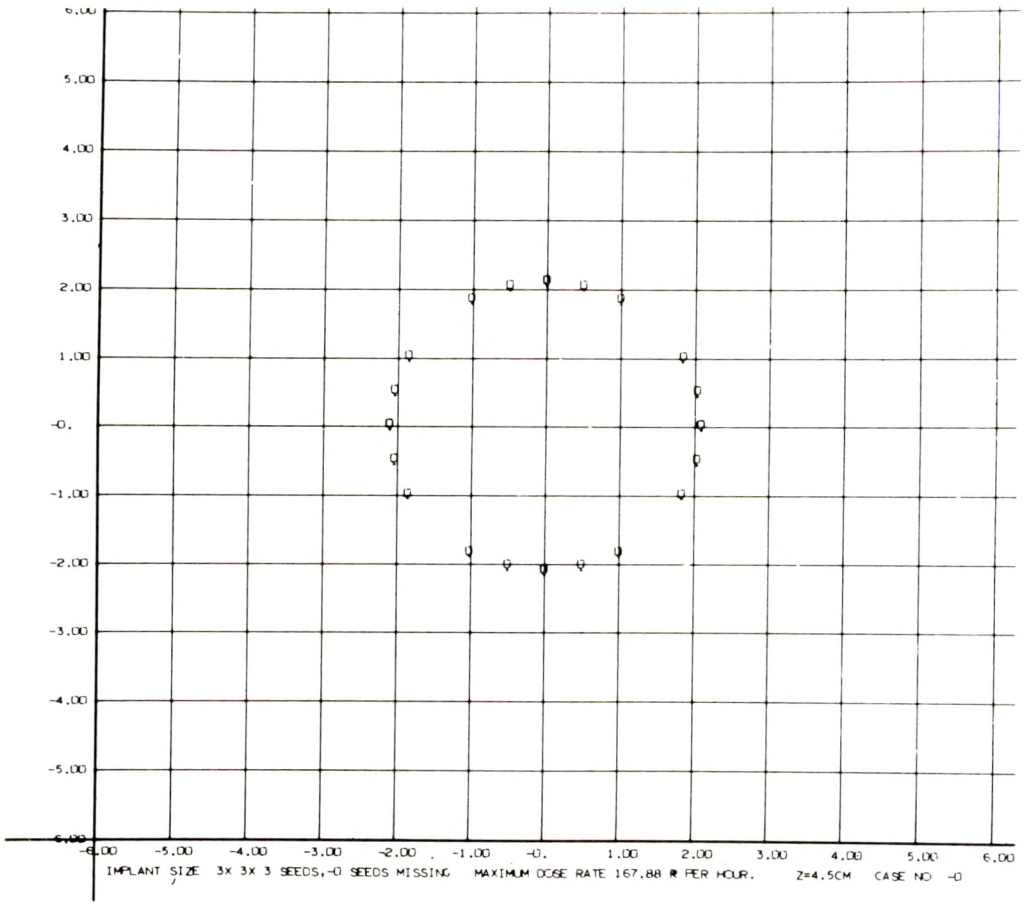


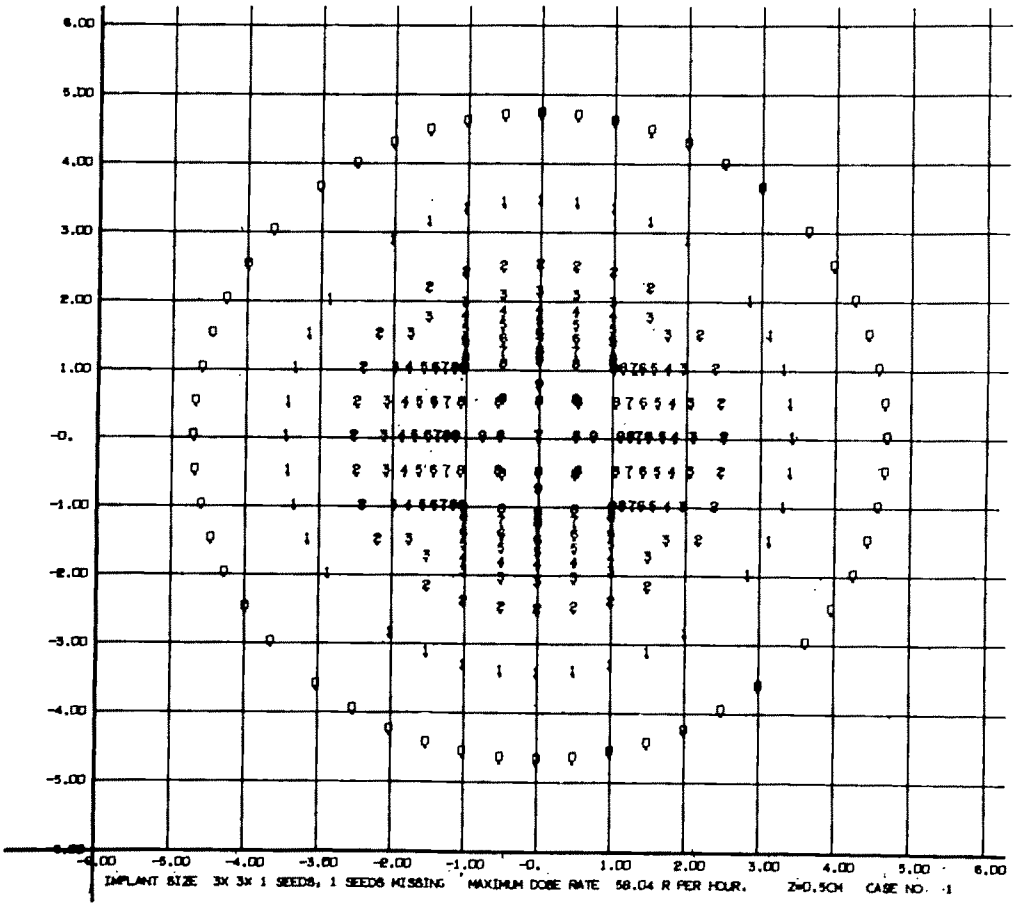
FIG. 8. Computer Output—Isodose Points for $3\times3\times3$ seed implant, $Z=4.5$ cm.

our data in the form of the conventional criteria which have been employed for dose specification for implants. Table 1 lists the milligram-hours needed to produce 1,000 rads for the minimum peripheral absorbed dose and 1,000 rads reference maximum absorbed dose 0.5 cm. from the plane of planar implants of the indicated areas. The ratio of minimum peripheral dose to reference maximum dose is also tabulated. Table 11 lists the number of milligram-hours necessary to produce 1,000 rads minimum peripheral absorbed dose as a function of implanted volume in cm.^{3} The number of milligram-hours necessary to produce a centerline peripheral absorbed dose of 1,000 rads and that necessary to produce a reference maximum dose of 1,000 rads are also listed, as well as ratios of centerline peripheral and minimum peripheral dose to the reference maximum dose.

COMPARISONS

For purposes of comparison, Figures 32*A* and 32*B* show the milligram-hours

FIG. 7. Computer Output—Isodose Points for $3\times3\times3$ seed implant, $Z=3.5$ cm.


IMPLANT SIZE 3X 3X 1 SEEDS, 1 SEEDS MISSING MAXIMUM DOSE RATE 58.04 R PER HOUR. Z=0.5CM CASE NO. -1

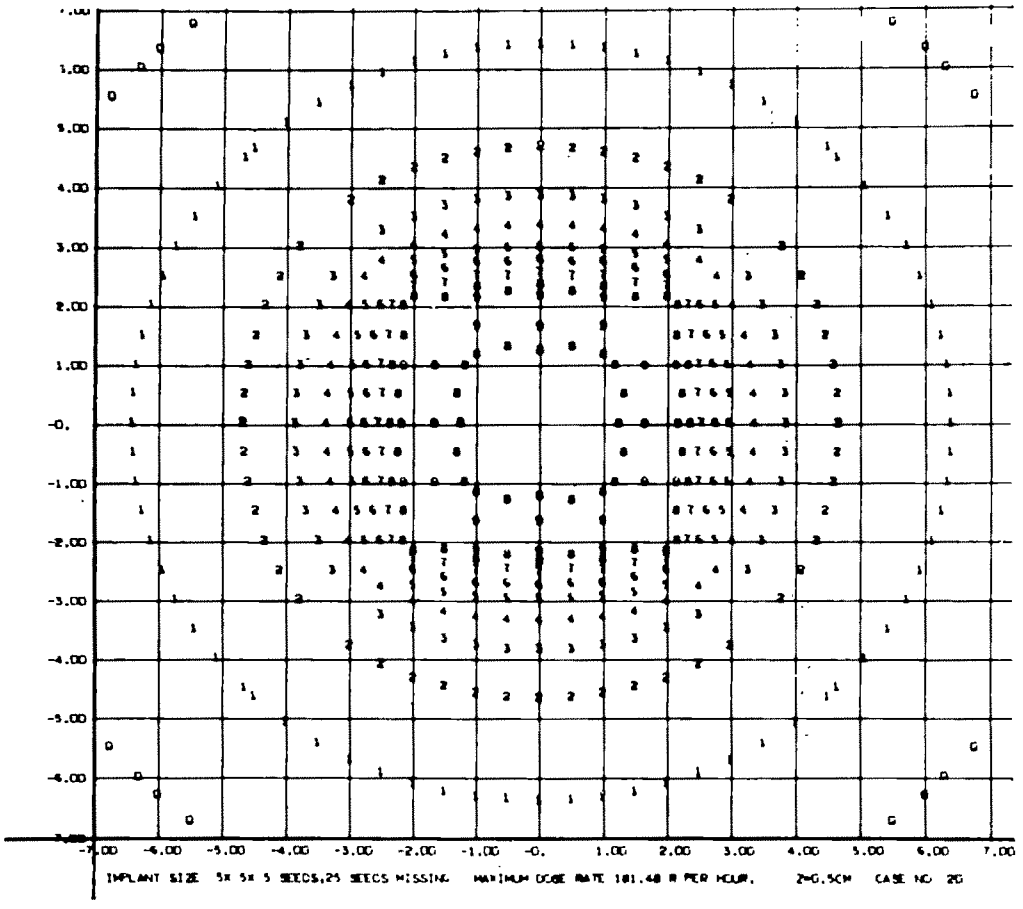

IMPLANT SIZE 5X 5X 5 SEEDS,25 SEEDS MISSING. MAXIMUM DOSE RATE 181.48 R PER HOUR. Z=0.5CM CASE NO. 25

Fig. 9. Computer Output—Isodose Points for 3×3 seed plane implant, central seed missing, $Z=0.5$ cm.

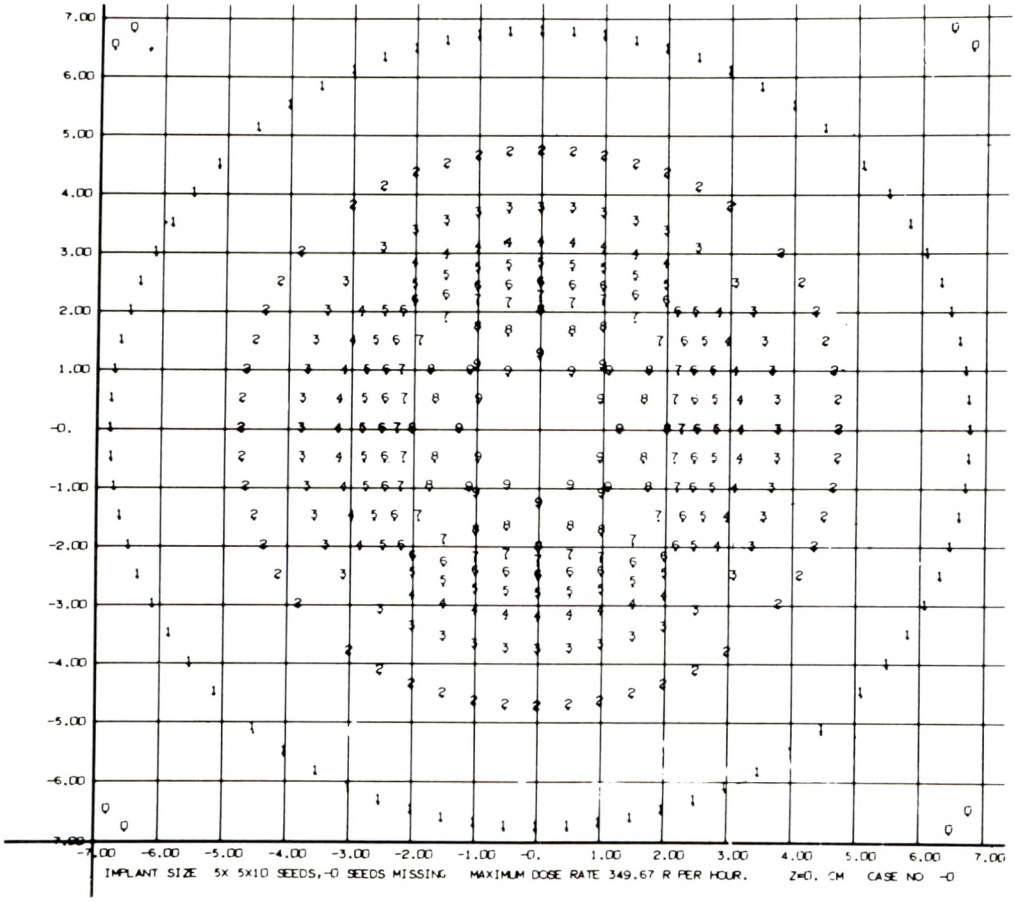


Fig. 11. Computer Output—Isodose Points for 5×5×10 seed oblong implant, $Z=0$ cm., plane perpendicular to long axis.

necessary to produce 1,000 r on the basis of the various systems. In the case of the Paterson-Parker system, the dose is 10 per cent above the absolute minimum, as is the case for the curves of Shalek *et al.*[19] The plot of Quimby's data is in terms of a peripheral minimum as is the case for our minimum peripheral plot. Our centerline peripheral is included to indicate some of the variation in peripheral dose which is much more completely shown in the isodose plots. A slight difference is due to the use of 8.4 r/mc-hr. at 1 cm. for all of the other plots, except ours for which the value 8.25[1] has been employed.

Roentgenograms of 3 specific cases which have been implanted relatively uniformly are shown in Figures 33, 34 and 35.

Fig. 10. Computer Output—Isodose Points for 5×5×5 seed implant, 25 central seeds missing, $Z=0.5$ cm.

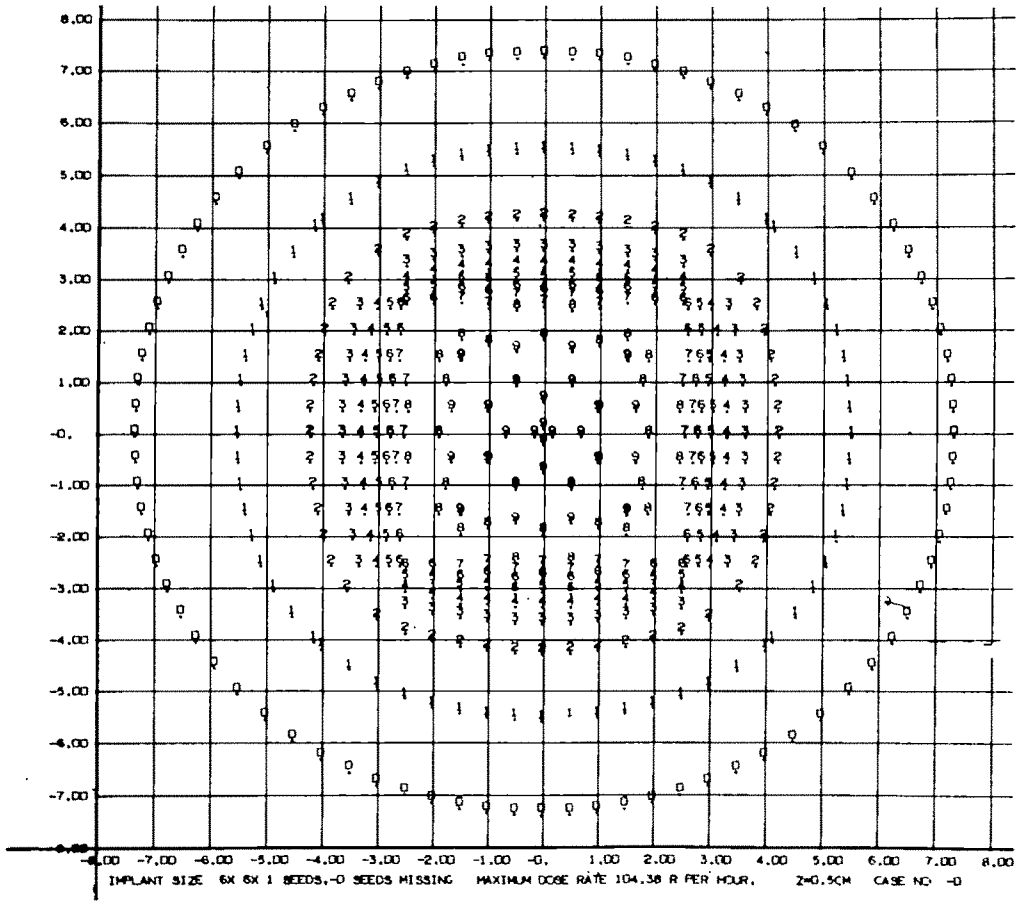


FIG. 12. Computer Output—Isodose Points for 6×6 seed plane implant, $Z=0.5$ cm.

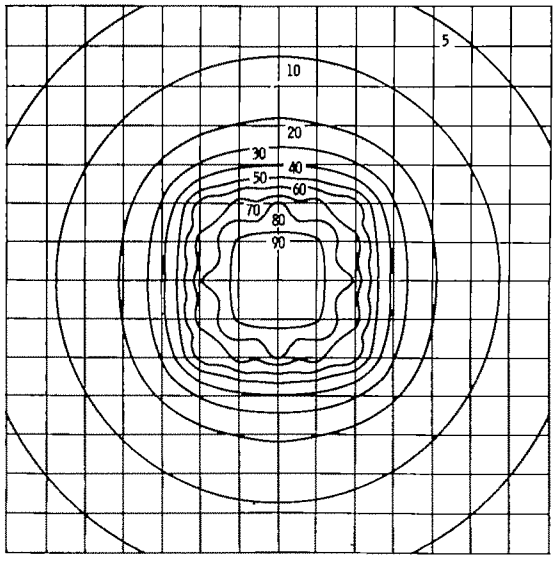


FIG. 13. Isodose Curves—5×5×5 seed cubic implant, $Z=0.5$ cm.

The dimensions of Case 1 (10×4.9) cm. in Figure 33 correspond closely to the 50 cm.^{2} area for which case a complete set of isodose contours exists. On the basis of minimum dose specification of the number of milligram-hours/1,000 roentgens, Table III gives a comparison of the exposures by the Paterson-Parker tables, Quimby's tables, and computations reported here. These differences are due to the differences in source distribution and differences in the specification of the reference dose. Figure 34 shows another patient treated with iridium 192 whose dimensions are close to (2×3×4) cm.^{3}, for which case isodose contours are also available. Table IV gives a dose comparison similar to that in Table III. A large radon implant is shown in the patient in Figure 35, whose dimensions are sufficiently close to (5×6×7.5) cm.^{3} for calcu-

TABLE I

PLANE IMPLANTS
MILLIGRAM-HOURS TO DELIVER 1,000 RADS
AT DESIGNATED POINT

Area (cm.²)	(1) Minimum Peripheral Dose Point	(2) Reference Maximum Dose Point	Ratio (1)/(2)
1	95	84	1.13
2	116	94	1.23
3	138	107	1.29
4	165	124	1.333
5	189	138	1.367
6	211	152	1.39
7	236	166	1.42
8	256	178	1.44
9	280	193	1.45
10	300	204	1.47
12	342	228	1.50
14	380	250	1.52
16	419	272	1.54
18	454	291	1.56
20	488	311	1.57
25	570	354	1.61
30	650	399	1.63
35	734	442	1.66
40	812	485	1.675
45	892	528	1.69
50	973	569	1.71

Dose points are defined in a plane 0.5 cm. from plane of implant. The sources are assumed uniform in strength and located on a 1 cm. grid.

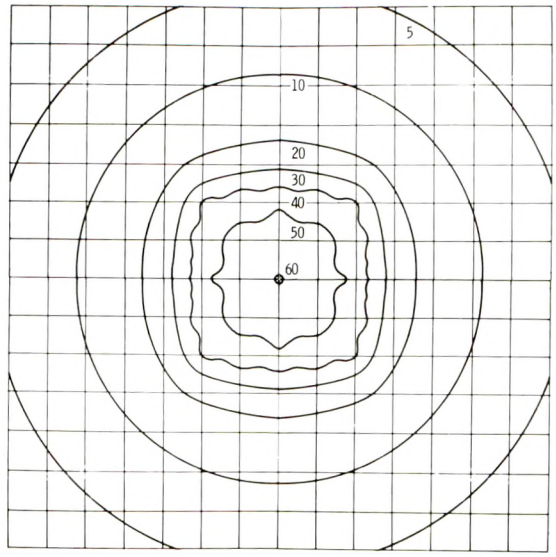


FIG. 15. Isodose Curves—5×5×5 seed cubic implant, $Z=2.5$ cm.

lated isodose contours to apply, although the source distribution does not have the uniformity of the grid specified in the calculations. Table v gives the minimum dose comparison. The computations reported here, including the absorption corrections, were made for radium or radon gamma rays. Similar computations are being car-

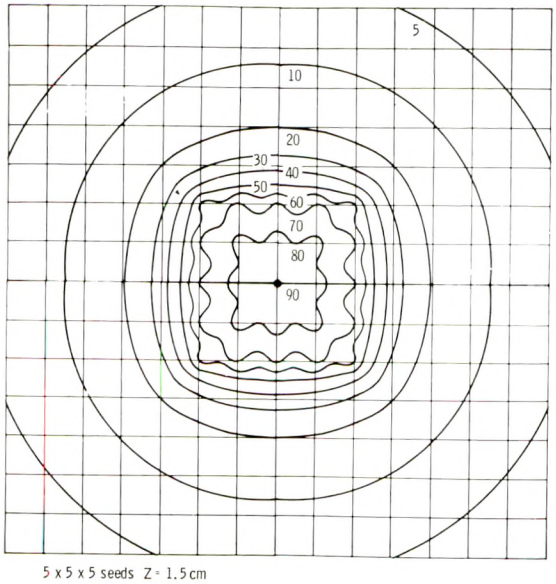


FIG. 14. Isodose Curves—5×5×5 seed cubic implant, $Z=1.5$ cm.

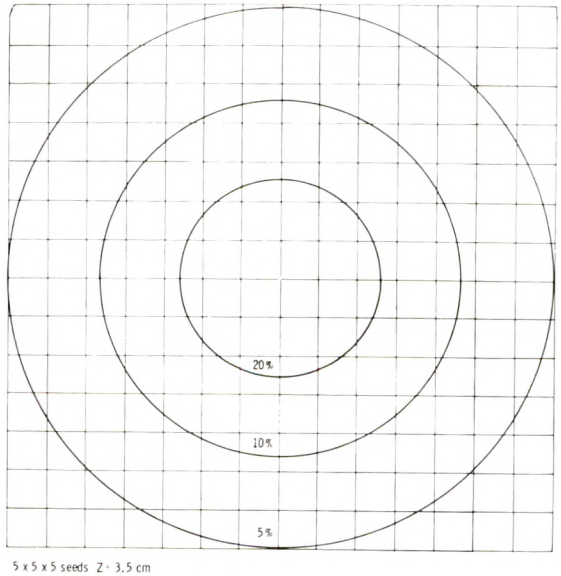


FIG. 16. Isodose Curves—5×5×5 seed cubic implant, $Z=3.5$ cm.

TABLE II

VOLUME IMPLANTS

MILLIGRAM-HOURS TO DELIVER 1,000 RADS AT DESIGNATED POINT

Volume (cm.³)	(1) Minimum Peripheral Dose Point	(2) Center Line Peripheral Dose Point	(3) Reference Maximum Dose Point	Ratio (1)/(3)	Ratio (2)/(3)
1	95	95	84	1.13	1.13
5	184	165	145	1.27	1.14
10	254	214	185	1.37	1.155
15	322	263	225	1.43	1.165
20	378	301	255	1.48	1.18
25	433	339	285	1.52	1.19
30	472	366	305	1.55	1.20
40	560	424	350	1.60	1.21
50	640	478	390	1.64	1.225
60	719	544	430	1.67	1.235
80	865	625	500	1.73	1.25
100	1,000	715	565	1.77	1.265
120	1,130	800	625	1.81	1.28
140	1,240	875	680	1.83	1.285
160	1,365	952	735	1.86	1.295
180	1,475	1,020	785	1.88	1.30
200	1,575	1,090	830	1.90	1.31
250	1,840	1,250	945	1.95	1.32
300	2,080	1,400	1,050	1.98	1.335
350	2,310	1,550	1,155	2.00	1.34
400	2,540	1,690	1,255	2.20	1.35

The sources are assumed uniform in strength and located on a 1 cm. grid.

ried out for the gamma-ray spectra of iridium 192 and other isotopes.

CONCLUSIONS

1. With the aid of rapid data-processing equipment, it is conveniently possible to provide complete isodose contours throughout radioactive implants. Particularly in cases where the dose distributions are expected to be irregular, it is important for

TABLE III

Plane Implant: A.H., Iridium 192
Diagnosis: Metastatic epidermoid carcinoma
Case I: Plane about 50 cm.²

MILLIGRAM-HOURS FOR 1,000 r AT SPECIFIED POINTS

Paterson-Parker	Quimby	Memorial (LSHR)	
net min. 705	maximum 548	min. periph. 1,010 (58%)	ref. max. 589 (100%)

TABLE IV

Volume Implant: K.H., Iridium 192
Diagnosis: Rhabdomyosarcoma of lower lip
Case II: Volume about 25 cm.³

MILLIGRAM-HOURS FOR 1,000 r AT SPECIFIED POINTS

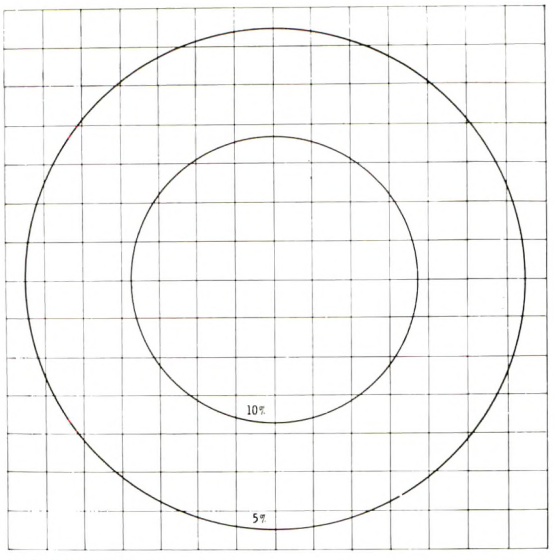
Paterson-Parker	Quimby	Memorial (LSHR)	
net min. 292	minimum 490	min. periph. 448 (66%)	ref. max. 295 (100%)

TABLE V

Volume Implant: O.G., Radon
Case III: Volume about 230 cm.³

MILLIGRAM-HOURS FOR 1,000 r AT SPECIFIED POINTS

Paterson-Parker	Quimby	Memorial (LSHR)	
net min. 1,280	minimum 1,608	min. periph. 1,800 (52%)	ref. max. 933 (100%)



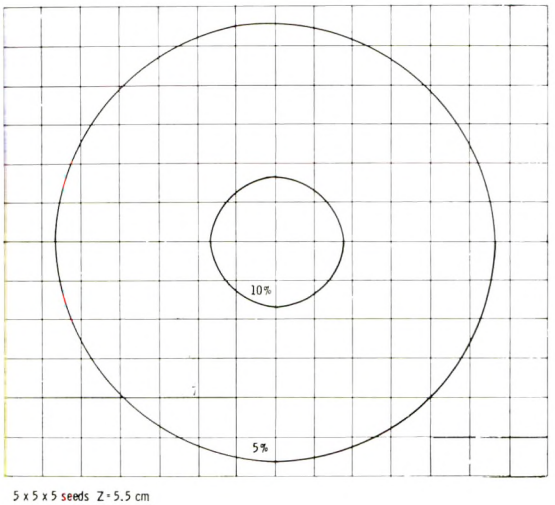


FIG. 18. Isodose Curves—5×5×5 seed cubic implant, $Z=5.5$ cm.

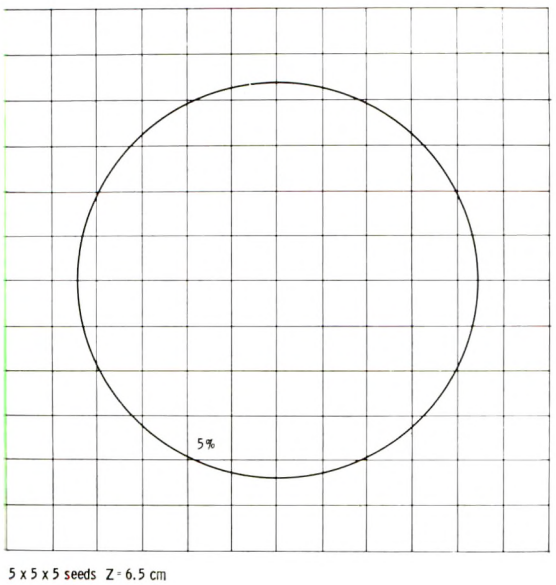


FIG. 19. Isodose Curves—5×5×5 seed cubic implant, $Z=6.5$ cm.

FIG. 17. Isodose Curves—5×5×5 seed cubic implant, $Z=4.5$ cm.

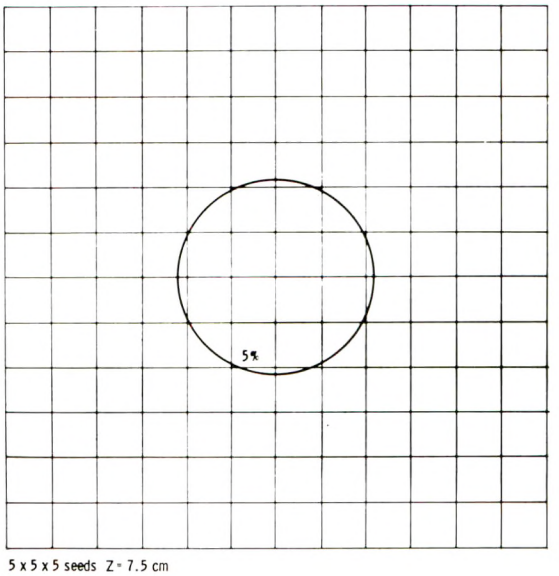


FIG. 20. Isodose Curves—5×5×5 seed cubic implant, $Z=7.5$ cm.

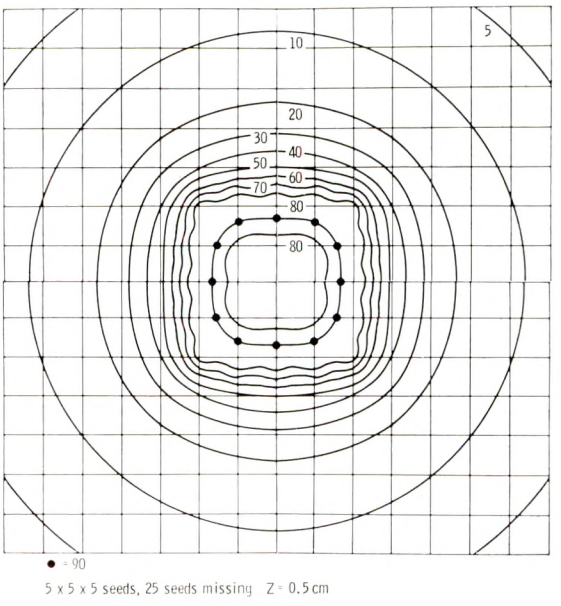


FIG. 21. Isodose Curves—5×5×5 seed cubic implant, 25 central seeds missing, $Z=0.5$ cm.

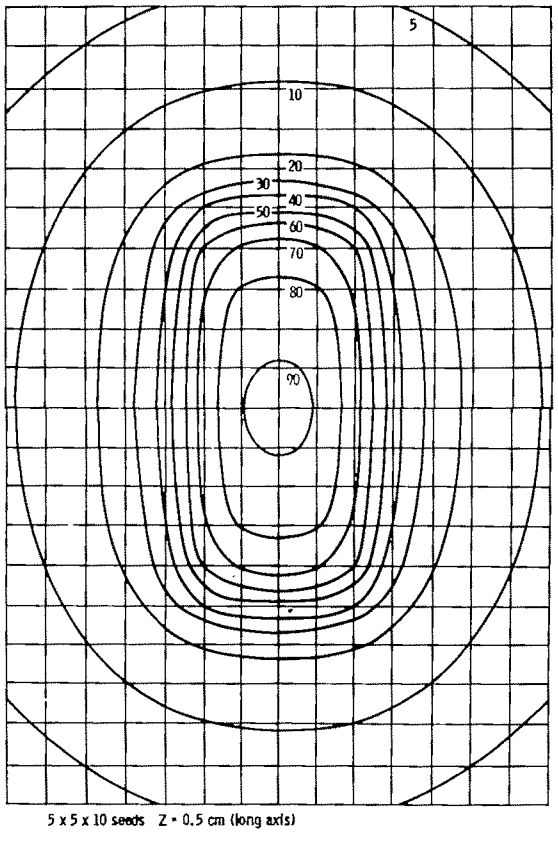


FIG. 22. Isodose Curves—5×5×10 seed oblong implant, long axis, $Z=0.5$ cm.

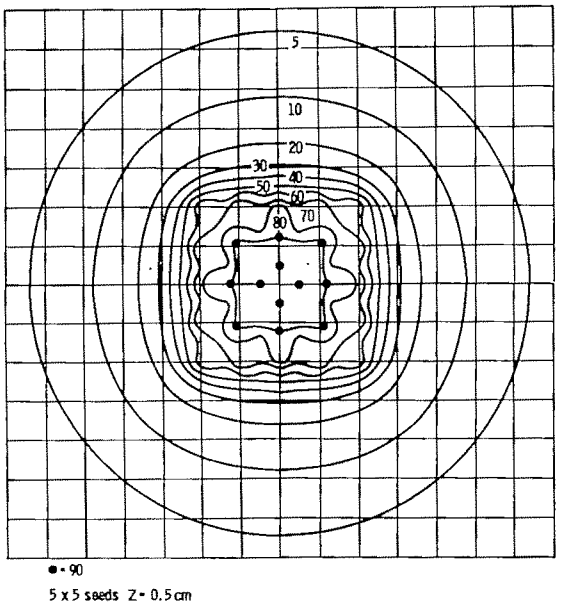


FIG. 23. Isodose Curves—5×5 seed plane implant, $Z=0.5$ cm.

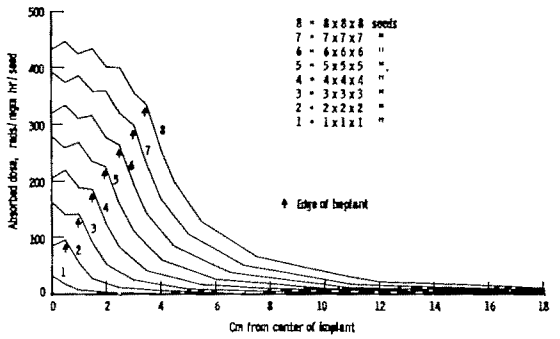


FIG. 24. Centerline Dose Profile: cubic implants.

the clinician to have such a map of these dose variations. Seed implants are prone to have major dose inhomogeneities, since many sources are involved and since the Paterson-Parker distribution rules are not easily followed under these circumstances.

2. Computing system methods make it feasible to include the absorption corrections for attenuation and scatter which should be considered internally for the case of large implants. Such corrections are essential in all cases, whether the implant is large or small, if correlation of dose with biologic effects on other organs may ever be desired.

3. It has been possible to define the total exposure required to produce a minimum peripheral dose in an unambiguous manner. The lack of ambiguity in this definition derives from the fact that it is feasible for a properly-programmed computer to search for the minimum peripheral dose. In these

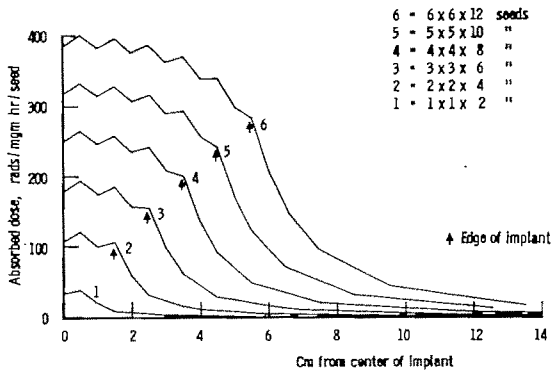


FIG. 25. Centerline Dose Profile: oblong implants, long axis.

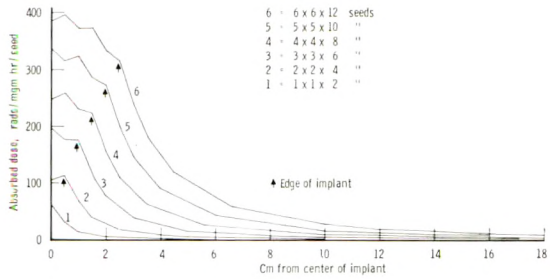


FIG. 26. Centerline Dose Profile: oblong implants, short axis.

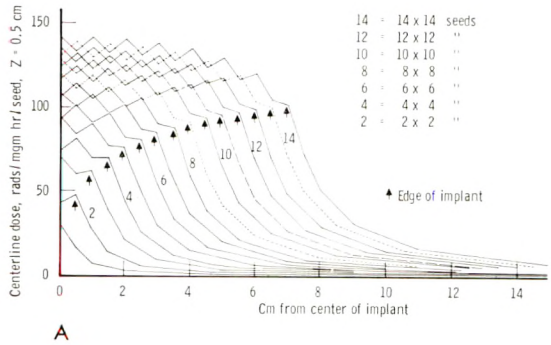


FIG. 27. (*A*) Centerline Dose Profile: plane implants, parallel to implant plane.

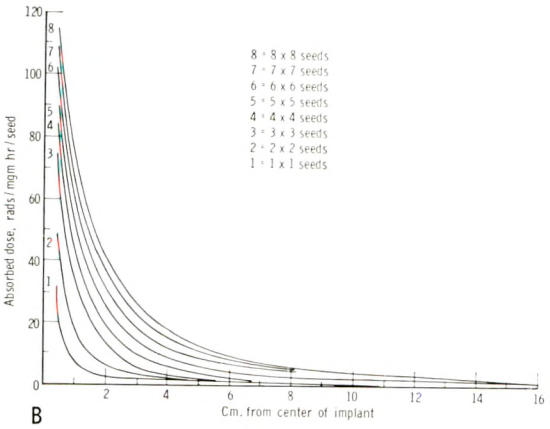


FIG. 27. (*B*) Centerline Dose Profile: plane implants, perpendicular to implant plane through the reference maximum dose.

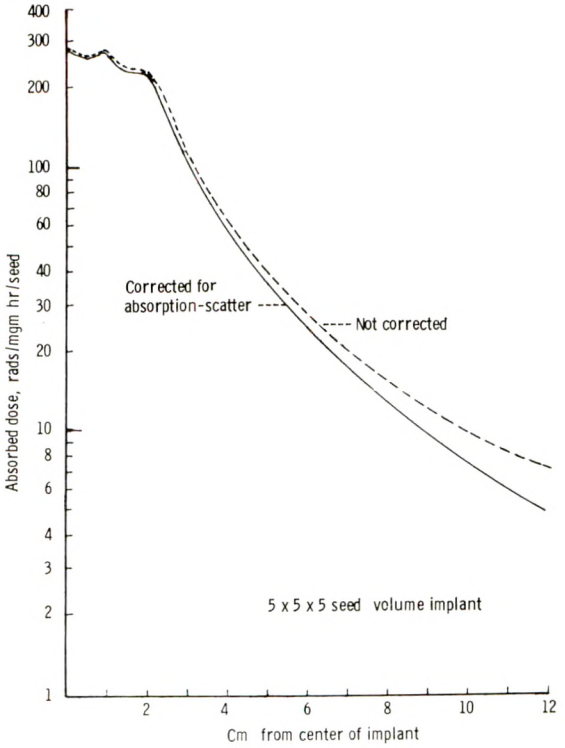


FIG. 28. Effect of absorption and scatter correction: centerline dose profile of 5×5×5 seed volume implant.

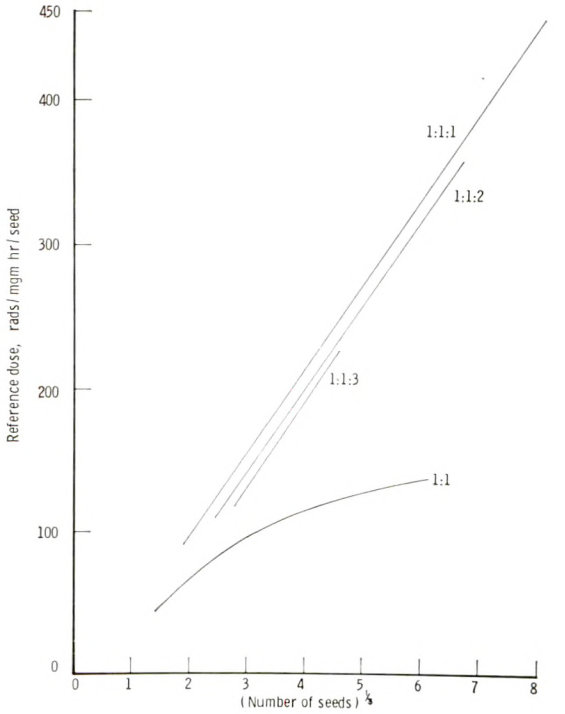


FIG. 29. Reference Maximum Dose Rate as a function of number of seeds for plane, cubic, and elongated volume implants. Ratios given are of the number of seeds on an edge of the implant.

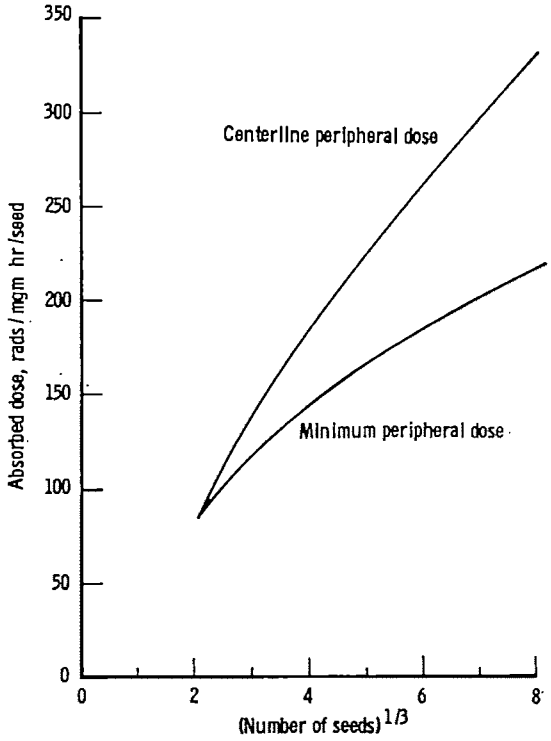


FIG. 30. Minimum and Centerline Peripheral Dose Rates as a function of number of seeds, cubic volume implants.

situations of extreme dose inhomogeneity, a minimum peripheral dose is difficult to specify with any precision without the complete isodose contours throughout the implant.

SUMMARY

An implant dosimetry system has been developed which can utilize any of a variety of the available rapid data-processing systems. This system provides the therapist with isodose contours throughout and

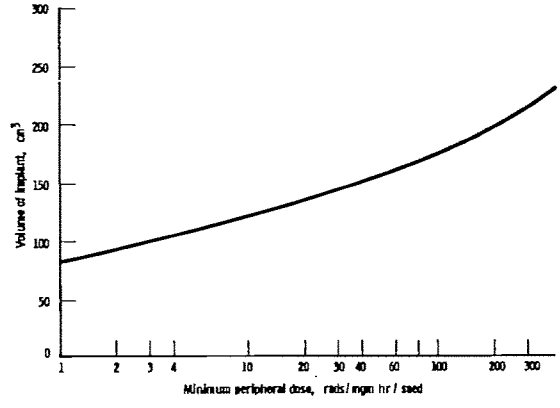


FIG. 31. Minimum Peripheral Dose Rate as a function of implanted volume, cubic implants.

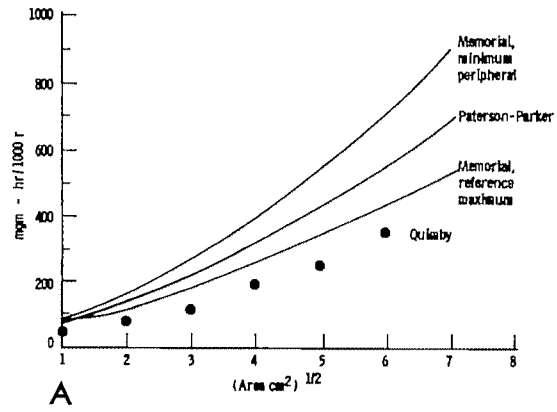


FIG. 32. (*A*) Implant Exposures for Specific Reference Doses for Plane Implants. This graph contains plots of the milligram-hours of radium or radon necessary to produce 1,000 r at a particular reference point in the various designated systems. Since the specification of reference point is not the same for all of these systems (see text), no discrepancy is necessarily indicated. This graph does show the correlation of the various systems in terms of their own reference points.

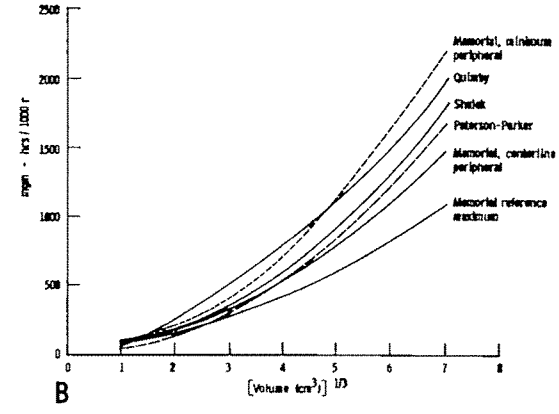


FIG. 32. (*B*) Implant Exposures for Specific Reference Doses for Volume Implants. This graph contains plots of the milligram-hours of radium or radon necessary to produce 1,000 r at a particular reference point in the various designated systems. Since the specification of reference point is not the same for all of these systems (see text), no discrepancy is necessarily indicated. This graph does show the correlation of the various systems in terms of their own reference points.



Fig. 33. Case I: Planar Implant.

beyond the implanted volume and makes dose information available for internal radiation therapy with the same precision as is available for external radiation therapy.

In this report the system is described which first has been applied to seed implants since their dose distributions are particularly extensive and inhomogeneous. A large variety of seed implants has been examined and complete sets of isodose contours have been produced for them. These data have also been analyzed in terms of minimum, maximum, and centerline doses which have been defined in an unambiguous manner.

The development of this sytem demonstrates the feasibility of the three dimensional comprehensive description of the internal dose distribution produced in the body by internally located sources. Because of the much greater information thus provided and the practicality of its application as continuously demonstrated in an increasing variety of implant cases, this system is recommended for use wherever computers are available. Programs and instructions can be obtained from the authors on request. For situations where computers are not available, the tables and isodose curves described here should be useful for seed implants, and other types of implants can be handled with either the Paterson-Parker or Quimby systems.

The library of analyzed source arrays is being continuously expanded and sets of isodose contours for specific arrangements can be made available.

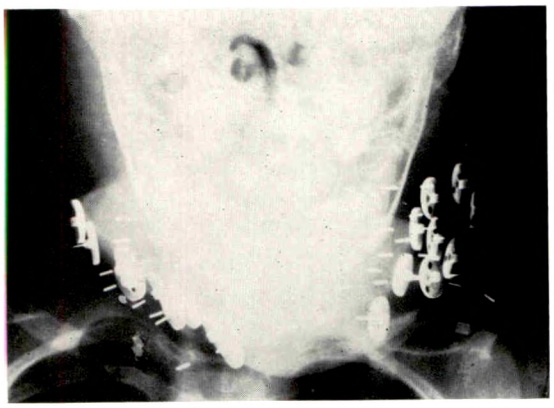


Fig. 34. Case II: Small Volume Implant.

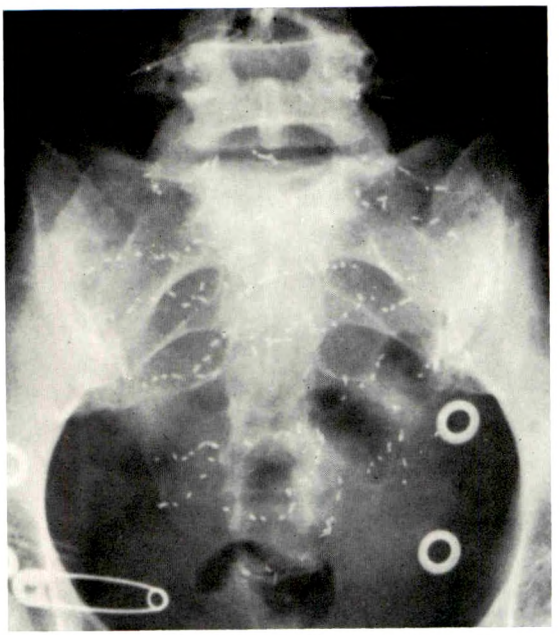


Fig. 35. Case III: Large Volume Implant.

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CAN ENDOMETRIAL CARCINOMA OF THE UTERINE FUNDUS BE ERADICATED WITH RADIUM THERAPY?*

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SOON after the value of radium as a treatment for cancer of the cervix was demonstrated, both radiologists and gynecologists began to experiment with the intrauterine use of this substance in the treatment of cancer of the endometrium. The inefficiency of many of the earlier techniques was described by one of us[5] in 1940 and a description of later developments together with a review of the literature was included in the gynecological section of the second edition of Pohle's textbook[8] published in 1950.

The description of the superior results obtained with the multiple radium capsule technique by Heyman[2] in 1927 revived the interest of many including surgeons who had condemned the use of preoperative irradiation on the basis that it was a needless waste of time.

TECHNIQUE

In 1935 we constructed some small capsules made of lead having a wall thickness of 1.0 mm. and each containing 6.25 mg. of radium. They were wrapped in a layer of self vulcanizing rubber. Although they produced some good results, it was very difficult to place them properly in the upper fundus and uterine horns and to pack the uterine cavity so that they would not slip out of place. A tight uterine pack was found undesirable because the discharge from the carcinoma was locked into the uterus during the 5 days of treatment and often produced pain and an elevation of temperature which necessitated the premature removal of the applicators.

The capsule which we use today was constructed in 1936 and has proved to be a practical and flexible device which can be fitted into uterine cavities of almost any shape. The original model is illustrated in Figure 1. The capsule is attached to a wire long enough to extend outside the cervix and its attachment is a hinged joint which allows rotation in only one plane. With a little experience one can usually insert applicators into both horns and then fill the fundus obtaining a suitable pattern as demonstrated by roentgenographic studies. A firm vaginal gauze pack which encompasses the lower loops of the wires holds the capsules in place and does not interfere with free drainage. The hinged capsules are removed at the end of 5 days and platinum or brass tandems, containing two or three 25 mg. segments and having a wall thickness

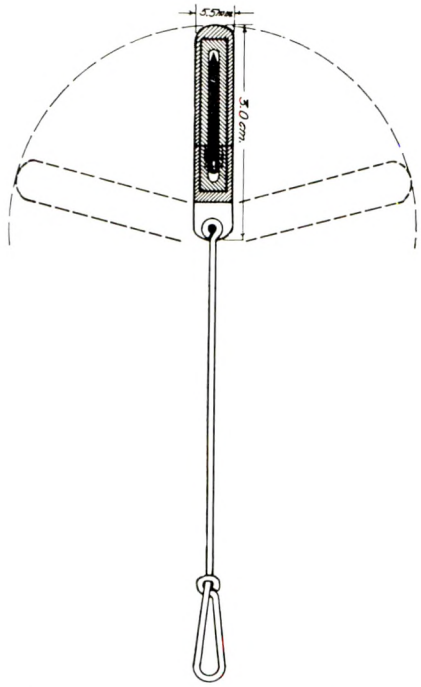


FIG. 1. Diagram of first intrauterine hinged radium capsule designed in 1936. In contains a 6.25 mg. steel radium needle surrounded by 1.0 mm. of platinum and an outer shell of aluminum which is hinged to a soft wire so that it can rotate through an arc of 180 degrees in only one plane.

* Presented at the Sixty-third Annual Meeting of the American Roentgen Ray Society, Washington, D. C., October 2–5, 1962.

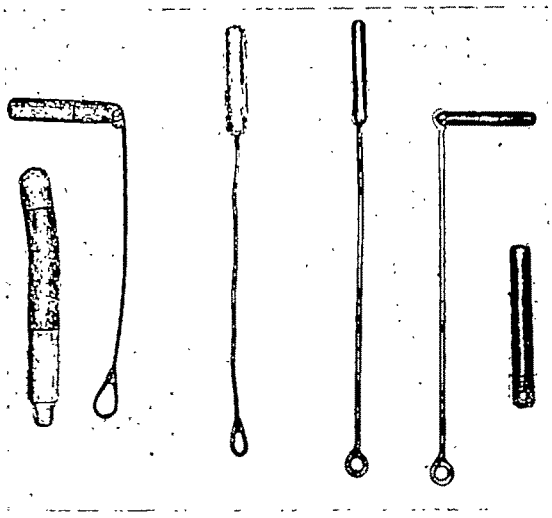


FIG. 2. Original hinged radium capsules and a three section 75 mg. tandem made with aluminum secondary filters are shown to the left of the midline. The more recently constructed hinged capsules and a two section 50 mg. tandem equipped with thin nickle plated brass secondary filters are shown to the right of the midline.

of 1.0 mm. and outer brass or aluminum shells (Fig. 2) are placed in the upper cervical canal and lower uterine segment for 24 hours. The total dose usually varies from 5,700 to 6,300 mg. hr. given in a period of 6 days except in large uteri where it may be as high as 9,000 mg. hr. During the past 2 years a better hinged applicator has been devised. The capsules have smaller diameters because the platinum shells are surrounded by thin layers of nickle plated brass rather than aluminum and the wires are stiffer and have smooth loops at the lower ends which do not become entangled in the gauze packs (Fig. 2). It is also possible to place them more easily in small uteri where the space is limited.

None of our clinically curable patients has received external irradiation. We do not believe that the doses which can be given safely to the pelvic cavity can actually eradicate metastatic lymph nodes invaded by endometrial carcinoma; also, we feel that the administration of larger doses (orthovoltage or supervoltage) render post-irradiation surgery more difficult as a result of pelvic fibrosis and other complications.

Similar opinions have been expressed in the more recent literature. Kottmeier and Gray[4] state that 4,000 gamma r is the maximum permissible dose for areas of rectal mucosa measuring more than 2 cm. in diameter in the average patient using the Radiumhemmet techniques and that a high rectal injury rate results in patients receiving more than a combined total dose of 6,000 r with external and internal techniques. Brunschwig and Daniel[1] state that preoperative tumor doses of 2,000 r to 4,000 r given with one million volt equipment have produced no unequivocal evidence to substantiate the value of this type of irradiation except in 1 case. Riva *et al.*[9] report that the million volt roentgen therapy has been omitted from the preoperative combined radiation technique at the Walter Reed Hospital because the complications produced rendered a proper dissection very difficult. Sala and del Regato[10] are among those who still believe that roentgen ray therapy alone constitutes the best form of preoperative irradiation. This opinion is based on the 3 year survivals in Stage I_1 cases of 87 per cent of 66 patients receiving preoperative roentgen therapy and 77 per cent of 40 patients receiving preoperative radium therapy. A 5 year survival rate of 79 per cent is given for the cases treated with roentgen rays but none is included for those treated with radium. The authors find it difficult to understand how such good results were obtained with roentgen rays alone following a tumor dose of only 4,000 rads given in 6 to 8 weeks. This is especially true when it is noted that pathological examination of specimens removed revealed residual tumor in 70 per cent of 68 cases treated with roentgen rays alone and in only 29 per cent of 31 cases treated with radium alone.

TECHNICAL DIFFICULTIES

Obviously, large submucous fibroids which fill most of the uterine cavity or obstruct the lower uterine segment constitute definite contraindications to intrauterine radium, but, since a successful diagnostic curettage cannot be done in these patients, they are usually subjected to surgery before

the diagnosis is made. We have been able to place hinged radium capsules in uteri containing rather large fibroids on several occasions without too much difficulty even though the cavities were deformed and displaced to one side (Fig. 3 and 5).

Perhaps our most troublesome problem has been encountered with the uterus which has been punctured by a Hegar dilator used in dilating the cervical canal. This accident is sometimes unavoidable when the uterus is antiflexed and partially fixed and the lower wall is very thin or infiltrated with malignant tissue. Radium capsules tend to follow the path of the dilator and great care must be exerted to see that they are not passed into the peritoneal cavity and left in place long enough to produce serious intestinal damage. In our clinic all intrauterine radium is placed while the patient is under a general anesthetic and after the vaginal walls and cervix have been thoroughly scrubbed with liquid green soap. The face of the cervix and the cervical canal are also coated with tincture of iodine. Under these conditions no cases of peritonitis have occurred in the small number with punctures of the uterine walls seen by us. As soon as the cervix is thoroughly dilated, a small curette is passed into the uterus to ascertain the size and shape of the cavity. If a puncture exists and the size of the uterus has been found to be normal on palpation, the easy insertion of the curette up to the handle makes the diagnosis. However, in very obese patients we have on a few occasions been unable to decide whether the uterus was large or whether a puncture existed. Under such conditions hinged capsules are inserted and, as soon as the patient's condition permits, roentgenograms of the pelvis in the anteroposterior and lateral positions are made after the intrauterine injection of lipiodol using the Rubin technique (Fig. 4). When the radium is found to be outside the uterine cavity, the capsules are removed and surgery is advised. In uteri removed a week or more after our unsuccessful attempt at radium insertion, the punctures have been found to be completely or almost completely closed.

DOSAGE

Since the size and shape of the uterine cavities and the thickness of the uterine walls are subject to wide variations and since the close approximation of the radioactive sources to the tumor tissue produces the best local results, the estimation of gamma r doses delivered by a variety of radium capsule configurations provides a different problem in each case. In 1948 Nolan and Natoli[7] worked out a plan for estimating point doses in and about a uterus of the type seen in a textbook of anatomy using an idealized symmetrical radium pattern. Those with sufficient time at their disposal may wish to wrestle with the problem of converting these data so that they can be applied to the many patterns used in uteri seen in actual practice. In our clinic, where the same technique has been used for some 25 years, the time is maintained at 6 days and the only variables consist of the number and position of hinged radium capsules and size of the tandems used to produce a pattern designed to eradicate the carcinoma known to be present without producing any irreparable damage to normal structures. For those who are shocked at our lack of interest in exact dosage calculations please allow us to put in a plea for the revival of the art of radiation therapy built on experience.

THERAPEUTIC VALUE OF RADIUM

Since in our experience Stage II cases are rarely cured with radiation, this presentation concerns only Stage I cases. Stage I_1 includes those which show no extension beyond the fundus of the uterus and are subjected to surgery about 6 weeks after irradiation, and Stage I_2 includes similar patients who are technically operable but are not considered good operative risks and are subjected to no surgical procedure other than a diagnostic curettage. Complications which may place a patient in Stage I_2 are such conditions as vascular disease, cardiac failure, diabetes, obesity and debility from old age.

Although we advocated preoperative radium therapy in 1935, we were asked to

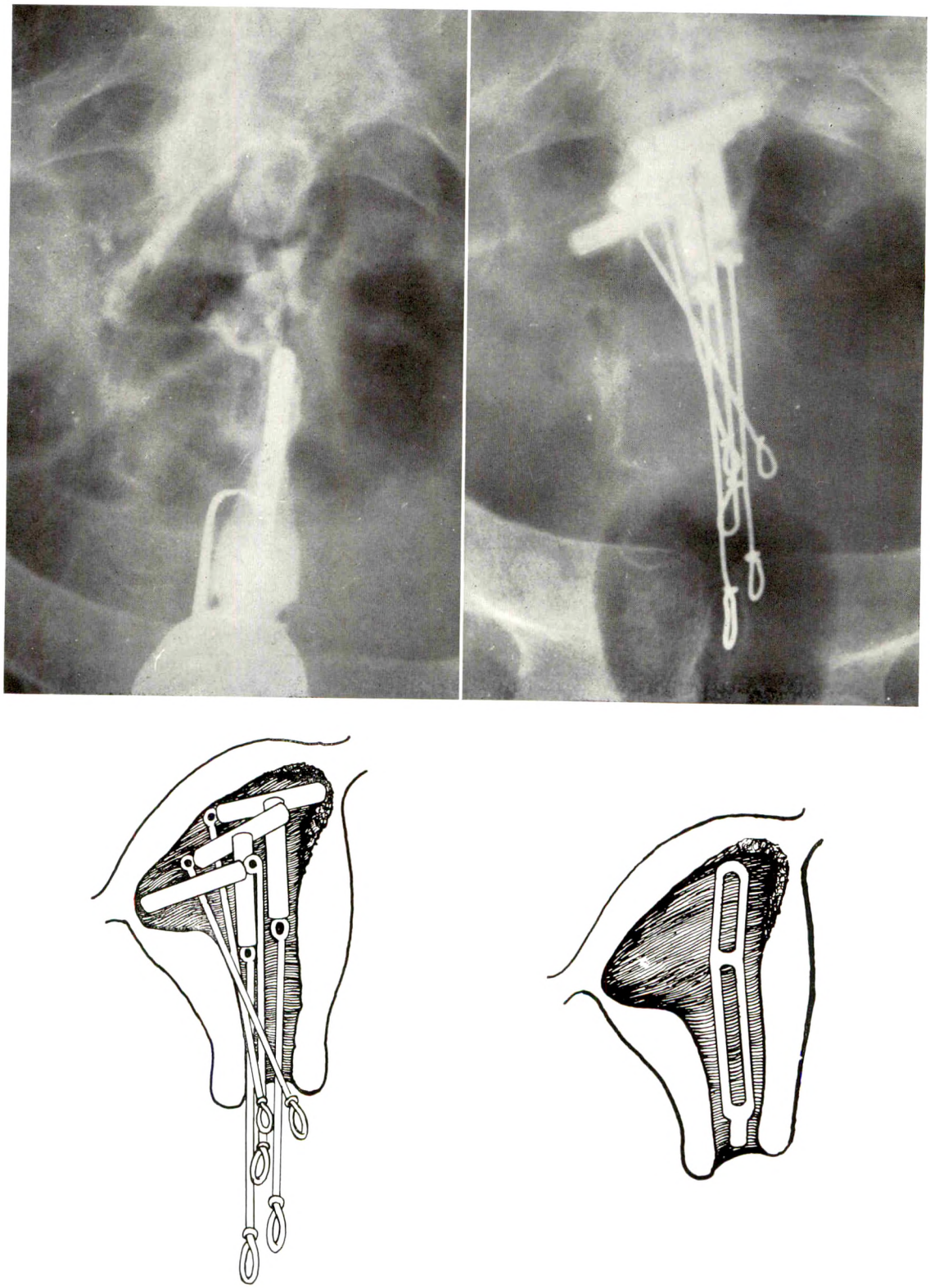


FIG. 3. The upper illustrations show roentgenograms of an atypical uterine cavity coated with hippuran and distended with carbon dioxide before and after the insertion of five 6.25 mg. hinged radium capsules for 5

treat a relatively small number of curable patients up until recent years. Many surgeons contended that radiation never produced permanent cures and that a hysterectomy should be performed as soon as the diagnosis of endometrial carcinoma was established. Table 1 shows the results in favorable cases selected from our old records to refute this statement. It has no statistical value because a complete survey of all of the patients treated so long ago was found to be impossible, but it does show that 5 favorable cases treated with the multiple capsule radium technique alone remained well for periods of 13, 15, 19, 20 and 25 years. It is also interesting to note that 5 patients whose uteri contained no cancer when surgically removed after irradiation were known to be free of cancer 9, 10, 20, 20 and 22 years later. The one case listed with residual cancer, found in the large postoperative specimen, is unusual in that recurrences in the vagina and parametrium were controlled with combined low intensity radium needles and roentgen therapy and she was known to be alive 18 years after her first visit with no radiation damage except a small ureterovaginal fistula. It seems evident then that

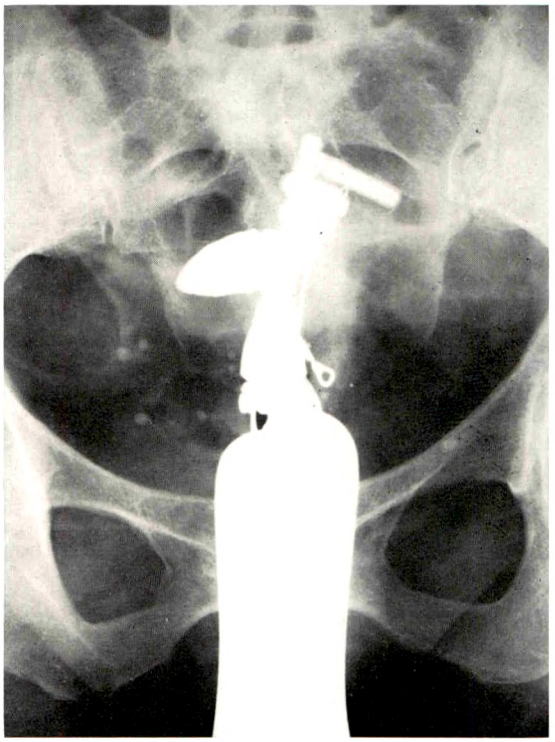


Fig. 4. Uterogram made after injection of lipiodol indicating that radium capsules have been inserted into peritoneal cavity through a rupture in the lower posterior uterine wall of an antiflexed uterus produced during dilatation of the cervix. No untoward symptoms occurred following immediate removal of the capsules.

Table I

CURE PRODUCED IN 11 STAGE I_1 CASES, TREATED 20 TO 27 YEARS AGO

Treatment Date	Histologic Grade	Size of Uterus	Post Radium Treatment	Outcome
1/31/36	I	normal	none	well 25 yr.
2/1/39	Adenocarcinoma	2×normal	hysterectomy, no cancer	well 22 yr.
12/24/42	Adenocarcinoma	1½×normal	hysterectomy, no cancer	well 20 yr.
12/4/41	III	1½×normal	none	well 20 yr.
10/25/41	I	normal	hysterectomy, no cancer	no cancer 20 yr.
3/4/35	I	moderately enlarged	none	no cancer 19 yr.
1/7/36	III	3×normal	hysterectomy, viable cancer	alive 18 yr.
12/1/36	I	small	none	well 15 yr.
6/14/35	II	moderately enlarged	hysterectomy, no cancer	well 10 yr.
10/13/38	I	normal	hysterectomy, no cancer	well 9 yr.
5/26/38	II	moderately enlarged	none	well 13 yr.

days. The drawings illustrate the multiple capsule pattern and the position of a 75 mg. tandem inserted on the sixth day for 24 hours. Fractional curettage indicated that the carcinoma was located in the upper left horn (Martin, courtesy of the *Southern M. J.*)

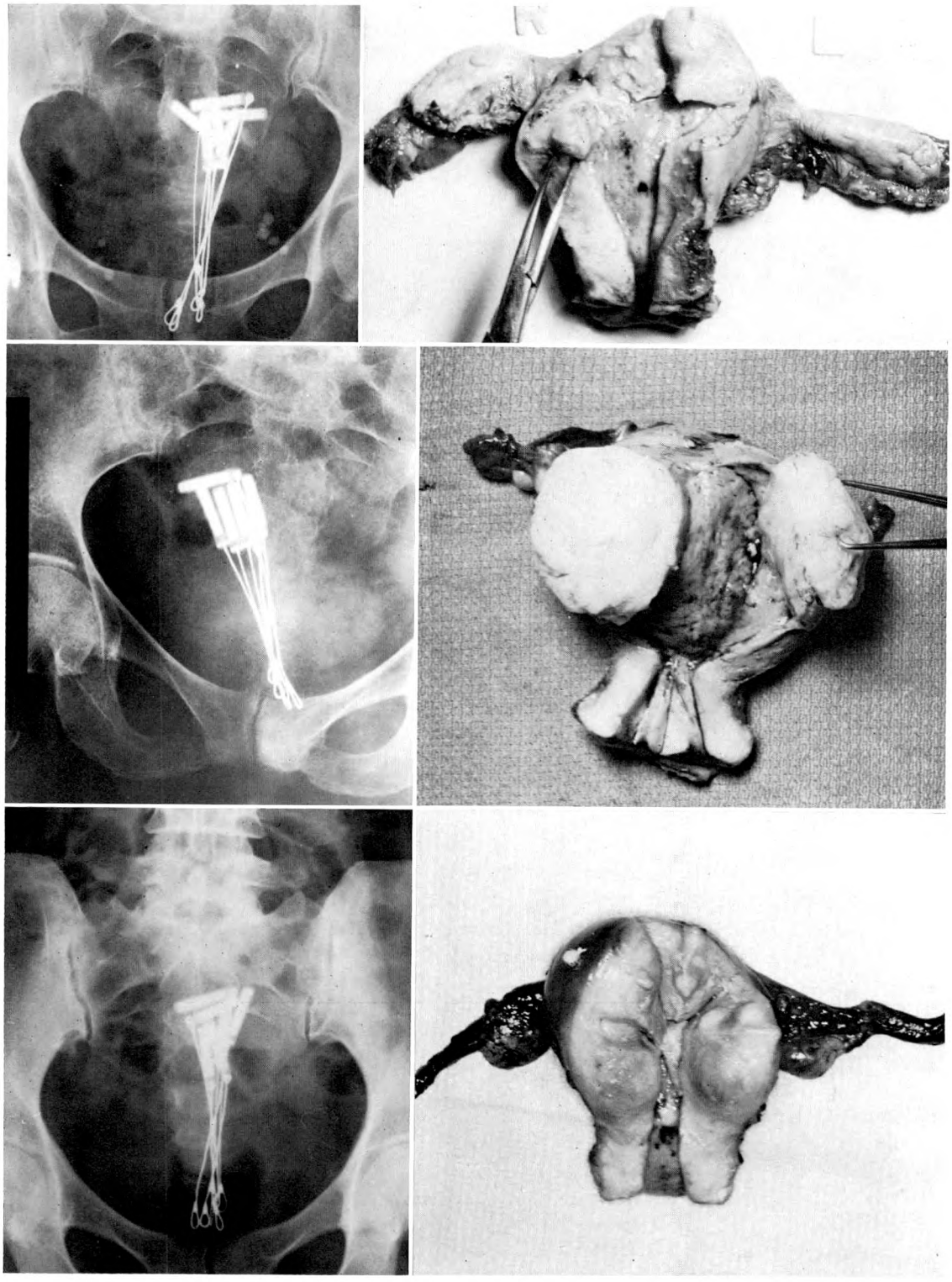


FIG. 5. Roentgenograms of hinged capsule patterns and photographs of opened uteri removed 6 weeks after completion of radium therapy in 3 cases of proven endometrial carcinoma. The lower uterine segments were treated with radium tandems in each case. All contained fibroids of various sizes. Pathologic examinations revealed no evidence of neoplasm except a small patch of nonviable cancer cells in the upper specimen. Reading from the top these patients have been alive and well for $7\frac{1}{2}$, 4, and 2 years, respectively.

endometrial carcinoma like cancer of the cervix can be cured for long periods of time when multiple radium applicators delivering large doses of radiation are placed in close approximation to it without the production of serious damage to surrounding normal structures.

STATISTICAL STUDIES

Our material is not large but we do have fairly adequate studies of 90 consecutive early proven cases treated during the past 18 years. Of these, 60 were placed in Stage I_1 and all had hysterosalpingo-oophorectomies about 6 weeks after radium therapy with examinations of the removed specimens made by competent pathologists. Roentgenography of the capsule patterns was a routine procedure and in many cases photographs of the open uteri were made in color.

A résumé of the pathologic reports for the entire group is shown in Table II. In 78.3 per cent no cancer could be detected in the resected uteri. In 6, cancer cells which showed definite evidence of radiation damage were still present but since the clinical results in these patients were all good it seems that they should be placed in the negative group, thereby labeling 88.3 per cent as nonviable. This leaves 7 (11.6 per cent) specimens in which patches of viable cancer cells were found. It seems possible that this figure may be reduced by more careful attention to technique, but it provides a good reason for advising post-irradiation surgery in Stage I_1 cases even though more than one-half of these patients should remain cancer free without it. This study also shows that the absence of cancer in the uterus improves the prognosis but does not necessarily mean a cured patient. In 1 patient a small metastatic mass in the omentum was found at operation and in another a metastatic cervical lymph node developed several months after surgery. Although these secondary lesions were treated, both patients are dead of the disease.

Table II

60 STAGE I_1 PATIENTS TREATED WITH RADIUM 3 MONTHS TO 18 YEARS AGO WITH POSTOPERATIVE PATHOLOGIC STUDIES

No cancer found in uterus in 47	78.3%
No viable cancer found in uterus in 53	88.3%
Adenocarcinoma elsewhere but uterus negative—2	
No viable cancer in uterus or other organs in 51	85.0%

Table III

STAGE I_1 CASES WITH NONVIABLE CANCER IN POSTOPERATIVE SPECIMEN

Recurrence	Well
1. none	3 mo.
2. none	8 mo.
3. none	1 yr., 3 mo.
4. none	7 yr.
5. none	9 yr.
6. none	9 yr.

Table III shows the good results obtained in the 6 cases having what we call residual nonviable cancer in the uterus. Different pathologists described the findings in different ways but all indicated the presence of the radiation changes in the cancer cells.

All of the cases except 1 with residual viable cancer in the uterus developed metastases after $1\frac{1}{2}$ years (Table IV). Only 1 of these is dead. In 2 patients we have been unusually successful in controlling the metastases; 1 is living and well at the end of 15 years following the use of electrosurgery and a low intensity radium needle implant for a small vaginal recurrence, the other is free of all symptoms with almost normal chest roentgenograms 7 years after her first treatment. Pulmonary metastases which appeared a little over 2 years ago showed a striking immediate response to a small dose roentgen technique described by one of us in 1959[6] augmented by the administration of progestational agents recently advocated by Kelley and Baker[3] (Fig. 6).

Most of our Stage I_1 cases have been treated during the past 5 years but the 27 treated 5 to 18 years ago are listed in Table V and have been carefully studied. Three patients died of cancer, 1 with recurrences in the pelvis and 2 with metastases in the

TABLE IV

STAGE I_1 CASES WITH VIABLE CANCER IN POSTOPERATIVE SPECIMEN

Recurrence	Outcome
1. none	well 3 mo.
2. none	well 1 yr., 3 mo.
3. none	well $1\frac{1}{2}$ yr.
4. pulmonary metastases	died $1\frac{3}{4}$ yr.
5. pulmonary metastases	alive and well 7 yr.
6. none	well 9 yr.
7. vaginal recurrence treated with radiation therapy	alive and well 15 yr.

chest, and 1 went abroad and is lost to follow-up. However, this leaves 23 (85.1 per cent) known to be alive and well for periods varying from 5 to $14\frac{1}{2}$ years. It is interesting to note that the salvage rate of 85.1 per cent is almost identical with the percentage of patients in the entire group of 60 cases which showed no viable cancer in the uterus or other parts of the body at or near the time of operation.

The 25 Stage I_2 patients treated during the same period are summarized in Table VI. The 5 year cure rate of 52 per cent is obviously too low; however, no death certificates for the 4 cases lost to follow-up are on file in the state Bureau of Vital Statistics and it seems most unlikely that all of them could have moved out of the state. If

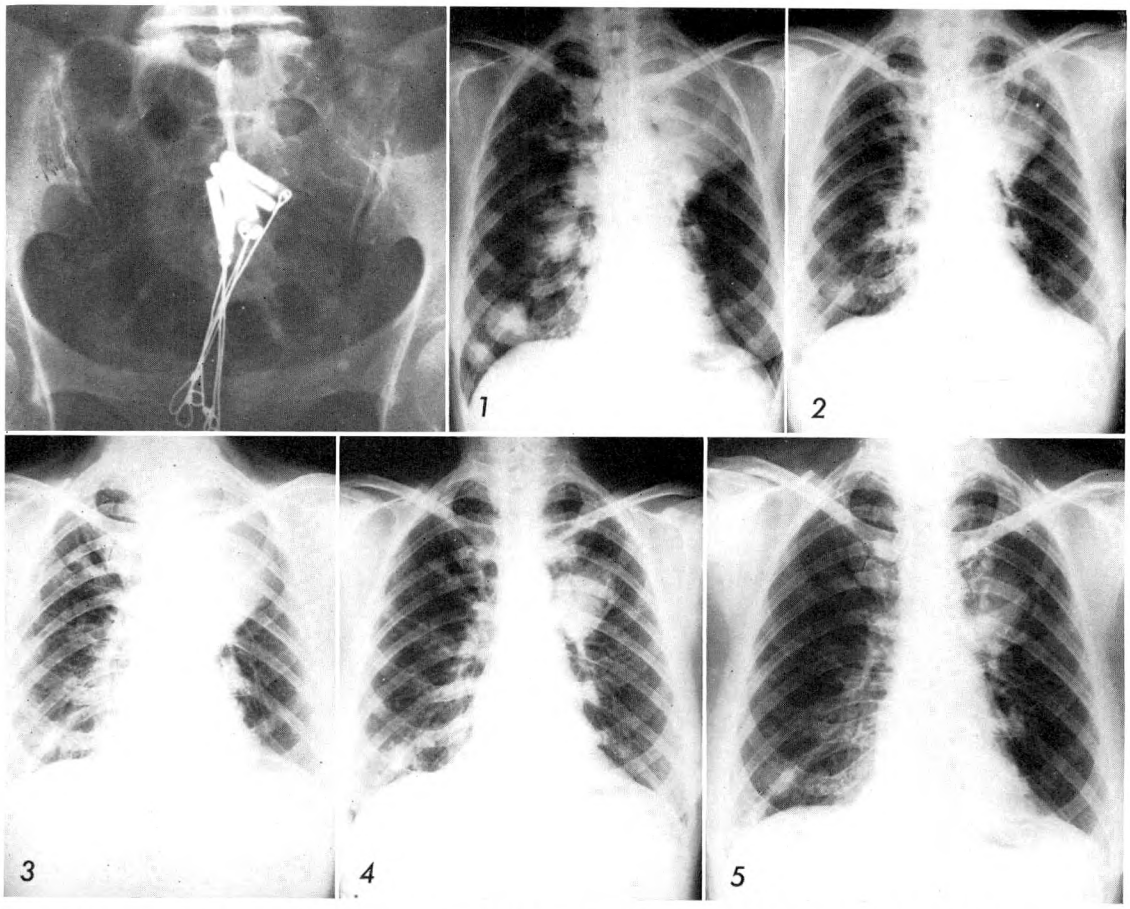


FIG. 6. Viable cancer found in the uterus resected 6 weeks after radium therapy. Cough and hemoptysis developed 5 years later when pulmonary metastases were discovered (1). Marked improvement (2) seen $2\frac{1}{2}$ months after administration of small doses of roentgen rays to lower right chest and upper mediastinum. Return of symptoms in 14 months followed by use of small dose roentgen ray technique over regrowth of mass in upper left chest (3). Marked reduction in size of mass 6 weeks later (4). After progesterone therapy marked improvement was noted in patient's general condition and further improvement in chest at end of 2 years (5).

Table V

27 STAGE I_1 CASES TREATED WITH RADIUM 5 TO 18 YEARS AGO WITH POSTOPERATIVE PATHOLOGIC STUDIES

Pathologic Report on Resected Uteri		Alive and Well 5 or More Years
no cancer found	20 cases	17
damaged residual cells	3 cases	3
viable cancer found	4 cases	3
	27	23 (85.1%)

they could be shown to be alive and well, the cure rate would rise to 68 per cent. The cure rates in this stage as reported by others are also much lower than for the Stage I_1 group. These patients are poor operative risks who not only have various other diseases but have a natural life span which often does not extend for 5 years beyond the time of treatment. Even so, the efficacy of radium is supported by the results obtained in the 13 successful cases in that 6 were living and well at 5 years, 2 at 8 years, 4 at 9 years and 1 at 13 years.

SUMMARY

The advantages of multiple hinged radium capsules designed in 1936 are described and cure rates of patients alive and well 13 to 25 years after treatment without the aid of surgery are tabulated to emphasize the fact that Stage 1 cases of endometrial cancer can be cured permanently with radium without the production of serious sequelae. A series of 90 early cases of endometrial cancer treated with radium during the past 18 years is reviewed and the results of a study of the surgical pathological specimens obtained in 60 Stage I_1 cases about 6 weeks after radium therapy are included. The absolute 5 year cure rates of 85.1 per cent in Stage I_1 patients, all of whom had surgery, and 52 per cent in the less favorable Stage I_2 group, none of whom had surgery, are similar to those obtained in other clinics and support our contention that intrauterine radium therapy when used carefully saves a great deal of time and produces results which compare favorably with those reported for other methods.

Table VI

25 STAGE I_2 CASES TREATED WITH RADIUM ALONE 5 TO 18 YEARS AGO

well 5 or more years	13–52%
died of cancer	4–16%
died of intercurrent disease, no cancer found	4–16%
lost to follow-up, no death certificate on file	4–16%
	25

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FRACTIONATED INTRAUTERINE RADIUM APPLICATIONS: USE OF A SMALL-DIAMETER AFTER-LOADING INTRAUTERINE APPLICATOR

PRELIMINARY REPORT

By G. R. RIDINGS, M.D.*
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IN TREATMENT of carcinoma of the cervix, it appears radiobiologically sound to fractionate the radium applications. Technical difficulties, including general anesthesia, and operating room expense are usually cited as "practical" reasons for compromising fractionation.

In our treatment program, those patients receiving a full radium course (earlier stages) have 4 weekly radium applications. This number made it desirable to alter our equipment so as to allow insertion of the radium tandem without general anesthesia (the vaginal application does not provide the same problem; therefore, is not further discussed in this paper).

It seemed reasonable that a tandem of very small outside diameter, by avoiding dilatation of the cervical os, would be well tolerated.[1,2] Others[3] have formulated after-loading techniques. Vaginal packing can be done with more efficiency and with less trauma than with the customary gauze.[4]

With these examples to guide us, we set about altering our intrauterine applicator. Figure 1 shows the equipment which has been in use during the past year.

The 4 mm. outside diameter of the tandem is sufficiently small that this tube can, for practical purposes, be passed as simply and atraumatically as a sound in any patient who can be sounded.

The patient, in the knee-chest position, is sounded. The depth of the uterine canal is measured. The rubber retaining ring is then slid to that distance from the tandem tip. The cervix is marked (with barium paste). The empty tandem is inserted to where the rubber retaining ring is against the cervix. The vagina is packed. Localization roentgenograms are taken. If these are satisfactory, the patient is taken to the ward and the silicone-rubber* tube with its contained radium is inserted and taped in place. Rectal and bladder dose measurements are then made.

The insertion of the intrauterine tube and the vaginal packing are greatly expedited by placing the patient in the knee-chest position, where there is natural ballooning and distention of the vagina. The foam plastic is a considerable improvement over cotton gauze. There is less trauma to the patient in the packing and withdrawal; it does not tend to "wipe off" the sensitive vaginal mucosa. Packing the fornices well requires less force and is considerably easier with this material. During the application the plastic maintains its resilience with gentle, outward pressure on the vaginal walls, not compacting as gauze tends to do; there is no tendency to develop mucosal pressure ulcerations; there can be more confidence that the original spacing will be maintained. In short, use of this material is a considerable contribution to the atraumatic nature of this technique of radium application.

Based on the depth of the uterine canal and the localization roentgenograms, the radium loading can be planned exactly, even before any radium is handled. The radium is then loaded into the plastic tubing in the radium room, affording its full protection, and in a carrier (with 3 inches of lead protection) is taken to the ward. There, in a few seconds, the radium is inserted into the hollow tandem and taped in

* Purchased from Dow Corning Corporation, Midland, Michigan.

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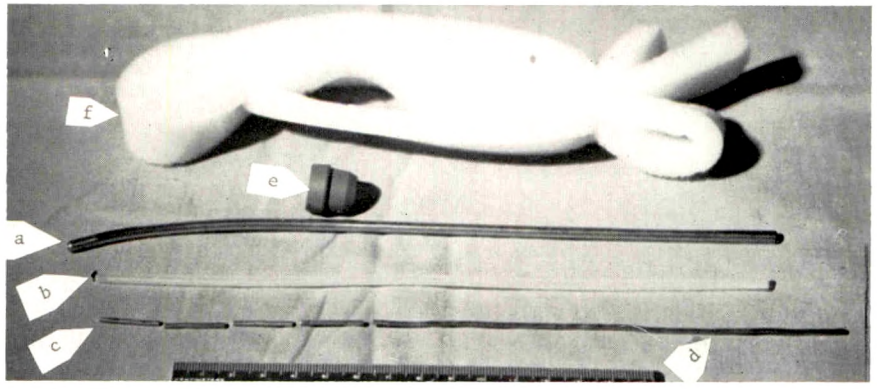


Fig. 1. (a) Stainless steel tubing: 4.0 mm. outside diameter, wall thickness 0.4 mm. (b) Silicon rubber tubing: 3.0 mm. outside diameter, wall thickness 0.6 mm. (c) Radium sources: total length 2.0 cm.; active length 1.8 cm.; outside diameter 1.85 mm. (d) Lead stylette (soldering wire). (e) Red rubber stopper. (f) Polyurethane foam packing material.

place. This eliminates all significant exposure of personnel except that received later by the ward nursing staff. We utilize usual time-distance instructions to minimize this.

Because of the simplicity of the procedure, if it appears that the radium application can be improved, there is no hesitation to repack, replace or otherwise change the application so that it is as nearly perfect as the patient's anatomy allows.

In spite of the high state to which anesthesiology has risen, it is still not improper to say that it is desirable to avoid the cost, morbidity, etc., attendant to general anesthesia if it is not required. There are a few patients who, because of stenosis cannot be sounded except under general anesthesia; these, of course, should be taken to surgery. Others can be handled better by the technique described in this paper.

Operating rooms are expensive—usually a significant part of the cost of treatment of cervical carcinoma. Also, in teaching institutions it is, unfortunately, too often impossible to secure operating room time when needed, resulting in delays and disruptions of treatment schedules. Significant violations of radiation therapy schedules reduce such treatments to radiobiologic guesswork. The simplified application procedure described here allows us to direct our attention to the primary problem; *i.e.* careful, accurate and consistent applications of radiations to the patient's cancerous tissues.

SUMMARY

It appears radiobiologically sound to fractionate radium applications in treatment of carcinoma of the cervix. Use of a small-diameter after-loading tandem allows this to be done in a simple and very satisfactorily atraumatic manner. Other advantages are less morbidity, less expense, less radiation exposure of personnel, increased precision in application, and increased consistency in treatment schedules.

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RADIOTHERAPEUTIC MANAGEMENT OF MALIGNANT TUMORS OF THE VAGINA*

By PAUL M. CHAU, M.D.†
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MALIGNANT tumors of the vagina may be primary or secondary. The urethra in the female is so intimately connected with the vagina in its entire length that the tumors originating primarily in the urethra present problems of management similar to those of lesions originating on the anterior vaginal wall. The location and the extent of the tumor in the various sites of the vagina and around the introitus dictate the radiotherapeutic techniques which are similar, irrespective of the histology of the lesion and even, to some degree, of the site of origin. The various types of interstitial and intracavitary radium techniques, alone or in combination with external irradiation, for these various subsites will be discussed in this paper.

The tumors manifesting themselves in the vagina and deserving radical radiation therapy may be classified in 4 categories (Table 1).

1. The squamous cell carcinomas originating in the vaginal epithelium.
2. The epithelial tumors of the urethra.
3. Metastases from adenocarcinomas of the fundus or cervix.
4. *In situ* carcinoma.

ROUTES OF SPREAD OF PRIMARY SQUAMOUS CELL CARCINOMA OF THE VAGINA

There is no anatomic barrier between the rectum and the bladder; therefore, they are often involved before the patient seeks help for vaginal symptoms, and, because of the poor tolerance to radiation of these organs, treatment difficulties are increased.

The mucosal membrane of the vagina is richly supplied with lymphatics. Inguinal lymph node metastases are frequent for lesions of the lower third of the vagina, more so if the disease extends into the vulva. The lymphatics of the upper vagina drain in a manner similar to those of the cervix. Through the rich communicating perivaginal lymphatics, spread of the malignancy to the paracervical, parametrial, and uterosacral regions is not uncommon even if the lesion is located in the lower part of the vagina.

I. THE SQUAMOUS CELL CARCINOMA ORIGINATING IN THE VAGINAL EPITHELIUM

Primary carcinoma of the vagina is rare, constituting 1 to 2 per cent of all neoplasms arising in the female genital tract.[1,3]

Squamous cell carcinoma has constituted 93.6 to 97 per cent of the primary carcinomas of the vagina in several reported series.[4,6,7,8] Livingstone[6] found that histologically 66 per cent were Grade II and 27.2 per cent were Grade III. In view of the moderate differentiation, squamous cell carcinoma of the vagina is believed to develop slowly, thereby existing a long time before it is diagnosed. Grade I verrucal-type lesions spread by gradual contiguous mucosal extension; however, tumors of average differentiation more often invade contiguous paravaginal tissues. In advanced cases with massive extravaginal extension, the lesion may remain localized to one wall or segment of the vagina.

Livingstone[6] found that lesions occurred in the vagina in the following order of frequency: lower third, 38 per cent; upper third, 31 per cent; middle third, 3.6 per cent; and widespread, 14.5 per cent. The posterior wall was the most common site (30 per cent). Extravaginal extension was noted in 57.3 per cent of the cases on initial

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Table I

DISTRIBUTION ACCORDING TO AGE AND RACE

Type of Lesion	Total No. of Cases	Under 40	40–49	50–59	60–69	Over 70	Caucasian	Negro
Squamous Cell Carcinoma of Vagina	36	2	6	9	10	9	24	12
Carcinoma of Urethra	25	1	3	9	7	5	24	1
Metastasis from Adenocarcinoma of Fundus	18	1	3	5	7	2	16	2
Carcinoma *in situ* of Vagina	6	2	0	2	2	0	6	0

examination, and 21.8 per cent had apparent inguinal metastases.

Thirty-six cases of untreated squamous cell carcinomas of the vagina were seen at the M. D. Anderson Hospital and Tumor Institute from December, 1948 to March, 1960. Twenty-four of these patients were Caucasian and 12 were Negro. Also seen were 4 cases of recurrent squamous cell carcinomas.

Primary squamous cell carcinoma of the vagina occurs relatively late in life compared to cancer of the cervix or endometrium. Our patients were mostly between 50 and 70 years of age; 11 patients were over 70 years of age, and the oldest was 83. The average age was 60 years.

The spread of a vaginal lesion has characteristics specific to its location.

A. *Introitus.* Infiltrating lesions of the introitus tend to invade the structures of the vulva with subsequent lymphatic metastases to the inguinal lymph nodes. Lesions arising on the lateral wall of the introitus extend, in addition, laterally into the loose connective tissue near the pubic arch. Anterior wall lesions at the introitus of the lower vagina invade the anterior urethra and, in more advanced cases, the tumor is fixed to either or both sides of the pubic arch.

B. *Anterior Vaginal Wall.* Because of the close relationship of the vesicovaginal septum, lesions of the upper two thirds of the vagina invade the neck and trigone of the bladder. Vesicovaginal or urethrovaginal fistulae make it more difficult to manage the malignancies and these cases have a poor prognosis. In such instances, any prognosis given is usually guarded because of the increase of lymphatic metastases within the pelvis.

C. *Lateral Walls.* The loose structures outside the vagina allow an unrestricted spread of the tumor when it penetrates through the vaginal wall to the paracolpos. Spread in one parametrium or the uterosacral ligament is to be expected because of the communication of the rich paracolpal lymphatics with the uterine lymphatics.

D. *Vault.* Vaginal carcinoma originating in the vault is more prone to spread through the lymphatics than by direct extension. The lymphatic drainage of the vault is the same as that of the cervix. The lower uterine ligaments and pelvic lymph nodes, therefore, should be considered potentially involved.

In patients who have had a hysterectomy, lesions of the vault invade the bladder early and have a bizarre lymphatic spread because of derangements of normal channels.

E. *Posterior Wall.* Lesions originating in this site are frequently seen localized to the wall of the vagina. Contiguous extension results in a mass within the rectovaginal septum. The rectal mucosa may be eroded with formation of a rectovaginal fistula.

The prognosis is poor when there is rectal involvement.

2. EPITHELIAL TUMORS OF THE URETHRA

The manner and mechanism of spread of cancer of the urethra in the female are very similar to those of primary vaginal cancers originating in the anterior wall or the anterior introitus. The tumors originating from the posterior urethra early involve the neck and trigone of the bladder.

Twenty-five patients were treated by radiation therapy from 1950 to 1960. Twenty-one patients were Caucasian and 4 were Negro. The ages ranged from 36 to 75 years, with an average age of 57. There were 17 cases of squamous cell carcinomas, 5 transitional cell carcinomas and 3 adenocarcinomas. Three were recurrent cases, 2 months to 3 years following surgical procedures. More than one third of the cases were early localized lesions located in the meatal region.

The following classification by anatomic sites is suggested:[2]

A. *Anterior Urethra (Perimeatal or Submeatal).* The lesion is located in the distal end of the urethra, either in the perimeatal or submeatal region. A subdivision into 2 groups is used for the purpose of selecting the method of treatment: (1) cases without involvement of the vulva. This group includes cases presenting some involvement of the introitus, anterior vaginal wall, or questionable pubic bone fixation and (2) cases with involvement of the vulva. These may have extension of the disease to either the labia majora, labia minora, posterior fourchette, clitoris, mons veneris, or definite fixation to the pubic arch.

B. *Posterior Urethra.* This group consists of lesions originating in the posterior urethra. These may be confined to the urethra alone but more often involve the neck or the trigone of the bladder.

C. *Entire Urethra.* These are extensive, localized lesions with submucosal infiltration or with ulceration into the anterior vaginal wall. It is not possible to determine whether the neoplasm originated in the urethra. Involvement of the bladder is often present.

D. *Entire Urethra with Regional Metastasis.* These lesions are far advanced with spread unilaterally or bilaterally through the paracolpal, parametrial, and paracervical regions, or with metastasis to the pelvic lymph nodes. The extensiveness of the disease precludes the exact determination of the site of origin along the urethra.

3. METASTASES FROM ADENOCARCINOMAS OF THE FUNDUS

The presence of vaginal metastasis in an untreated adenocarcinoma of the fundus indicates widespread disease and has an extremely poor prognosis. These patients are treated for palliation.

Patients who have had a hysterectomy and later develop metastasis in the vagina are thought to have a better prognosis. The incidence of vaginal metastases following hysterectomy is approximately 10 per cent. Patients treated by intrauterine and vaginal radium prior to hysterectomy have a very small incidence of vaginal metastases.[9]

Eighteen cases of metastasis from adenocarcinoma of the fundus after hysterectomy performed in another hospital were seen from April 21, 1950 to January 27, 1959. In 39 per cent, the vaginal lesion occurred within 12 months while in 55 per cent it occurred 12 to 36 months after the hysterectomy.

The location of the metastases was most often in the the upper vagina. This is at variance with other series.[5]

A comprehensive therapy should include the entire vagina but this is not always practical. In certain sites, such as the introitus, a second metastasis could be easily managed. In patients having more than one vaginal lesion, therapy should include the entire vagina.

The presence of other metastases in the pelvis or elsewhere in addition to the vaginal lesion means that palliative treatment is indicated.

4. IN SITU CARCINOMA

Carcinoma *in situ* of the vagina is often multicentric. The 6 patients treated were under the age of 70 with 2 patients under 40.

In situ carcinoma or invasive cancer of the cervix is frequently noted before the appearance of the lesion in the vagina. Less commonly, the cervical cancer may appear after the *in situ* cancer of the vagina. One patient later developed a squamous cell carcinoma in the urinary bladder.

In situ lesions can eventually develop into invasive cancer and therefore treatment should be as vigorous as that given to the latter. A single biopsy should not be relied upon; multiple biopsies should be obtained to rule out invasiveness.

5. LATE METASTASES FROM CERVICAL CANCER

Two types of these cases are seen. In one, the vaginal metastasis is the only manifestation of the disease, and in the other type there is recurrence in the cervix or the pelvis. In the first type, radical treatment is indicated.

RADIOTHERAPEUTIC TECHNIQUES ACCORDING TO SUBSITES

1. TUMORS LOCATED AT THE INTROITUS

Various techniques of treatment for these tumors are shown in Figure 1. For the lesions located on the fourchette, cone therapy is very effective. Protraction of the treatment is required because the vulva does not tolerate radiation well. An air dose of 5,000 to 6,000 r in 10 to 15 days is generally found satisfactory with the 60 kv. Chaoul unit. Thicker infiltrative lesions are given the same dose with either 140 kv. or 250 kv. in 3 weeks. A curved single plane radium implant may be selected for a lesion which is extending upward into the posterior wall of the vagina since there is less satisfactory depth dose with cone therapy.

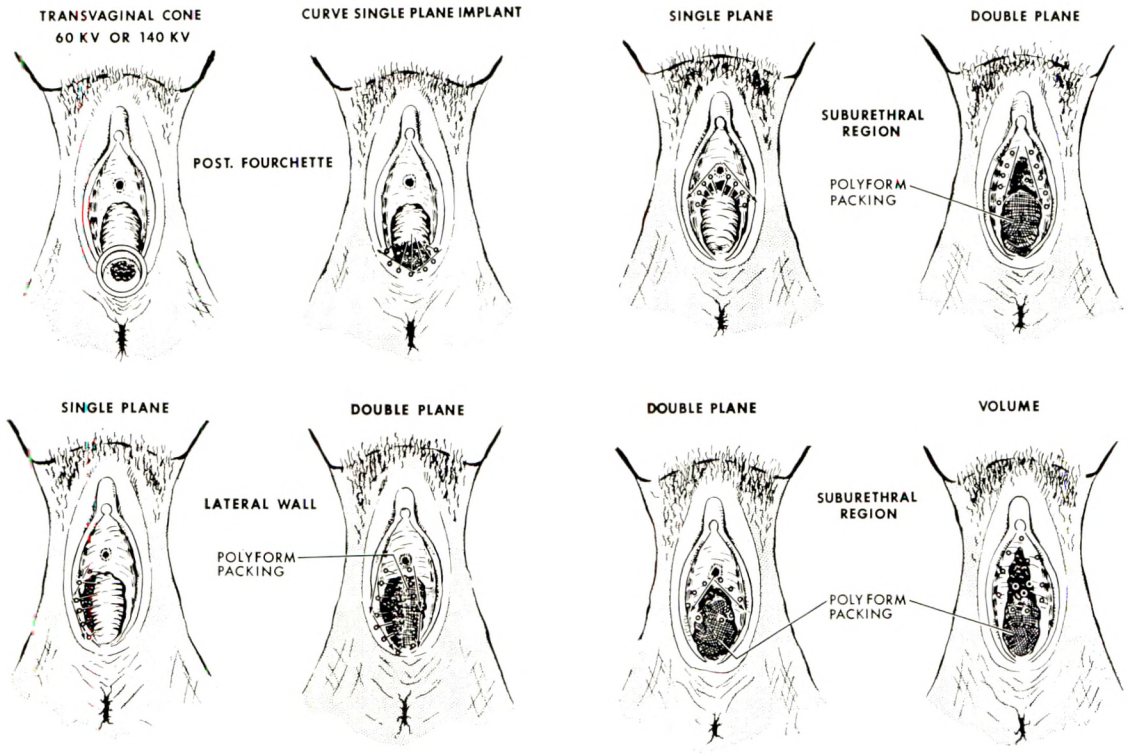


Fig. 1. Techniques of treatment for tumors at the introitus.

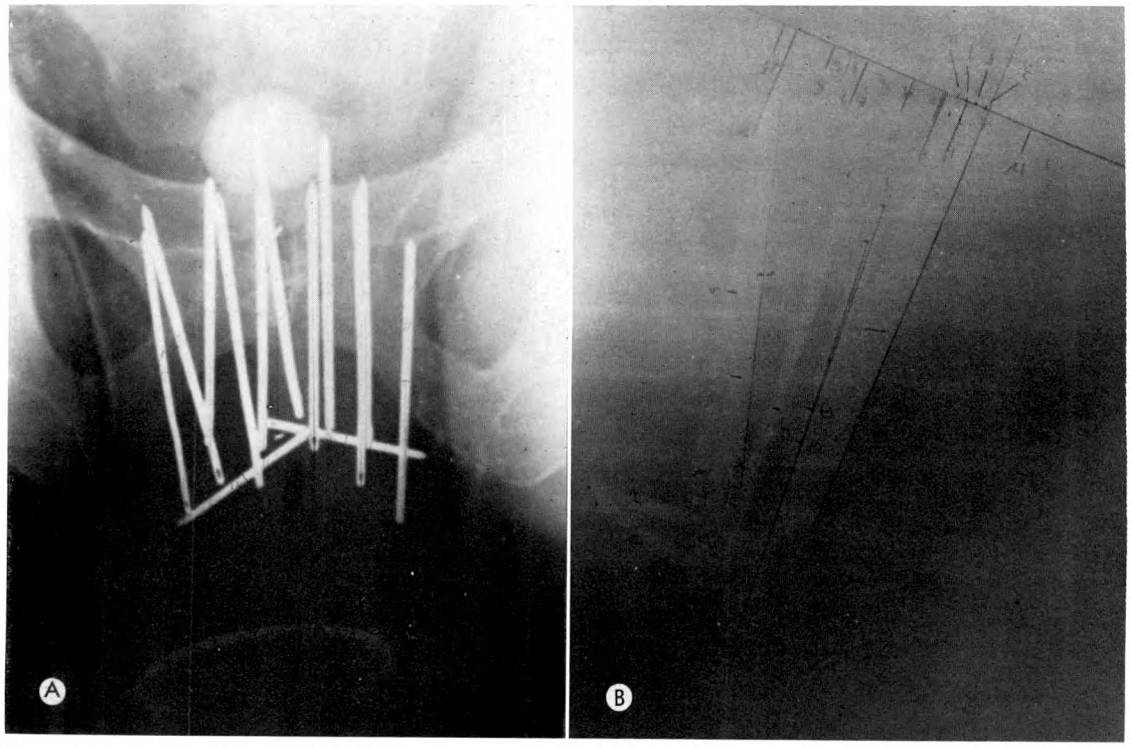


FIG. 2. Case E. V., a 45 year old white female, was seen on February 13, 1958 for a squamous cell carcinoma of the vagina. A nodular tumor, involving the lower two-thirds of the anterior vaginal wall, was noted in the suburethral and the periurethral region for a width of 2 cm. (*A* and *B*) The patient was treated by a two plane implant consisting of seven 3 mg., four 1.5 mg. and two 1 mg. radium needles, delivering 7,750 r in 122.5 hours. Two small ovoids with 15–15 mg. radium were applied for 48 hours to augment the dose at the upper vaginal wall. Six months after treatment a necrosis, which lasted for about 2 years, developed on the lower anterior vaginal wall. She was last seen on October 30, 1961, 3 years after treatment, without disease.

A radium implant is the treatment of choice for lesions at the meatus, lateral and suburethral area of the introitus. For a superficial tumor, a single plane implant is sufficient. For a larger and infiltrative tumor, either double plane or volume implants are used. A dose of 5,000 to 7,000 r in 5 to 7 weeks has been found effective. The complication from this treatment is occasional local necrosis occurring about 6 months to 1 year following the treatment. This necrosis may persist for 1 to 2 years, causing the patient considerable distress, but eventually it heals with conservative management.

Radium implants are not advisable for tumors already involving the vulva because adequate treatment becomes questionable. For similar reasons, in tumors with fixation to the pubic arch, a radium implant alone will not be sufficient. Our experience in such patients treated by radium implant alone revealed a poor result in the control of the primary tumor.

Advanced cases should be treated by external irradiation alone or supplemented with radium therapy. A technique with the patient in a knee-chest position spares the rectum while satisfactory irradiation of the primary tumor is obtained (Fig. 4*B*).

ILLUSTRATIVE CASES

CASE C. W., a 62 year old female, was treated in August, 1949 in this institution for a Stage II squamous cell carcinoma of the cervix by 2×72 hours intracavitary radium of tandem with 10-10 mg. and two vaginal ovoids with 21-21 mg. In addition, she received parametrial irradiation of 4,000 rads to the right and 5,000 rads to the left pelvis through a 400 kv. unit.

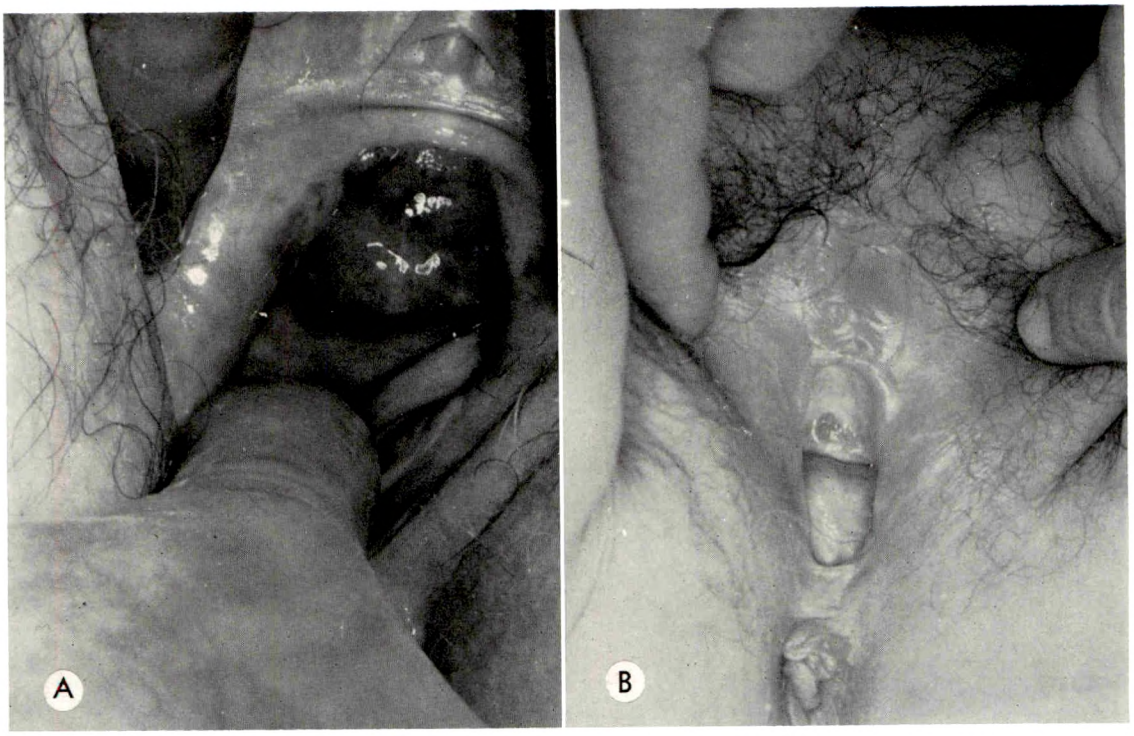


Fig. 3. Case M. W., a 56 year old white female, was seen (*A*) on October 22, 1956 with a tumor surrounding the urethral meatus which on biopsy was diagnosed as squamous cell carcinoma. A dose of 5,470 r in 100 hours was delivered by a volume radium implant. On January 15, 1956 bilateral ilioinguinal lymph node dissection was performed because of palpable lymph nodes in the right groin, which proved to be negative. (*B*) This patient was last seen on October 17, 1961 with no evidence of disease.

Examination on March 6, 1951 disclosed a polypoid 1.5 cm. firm nodule located 1 cm. posterior to the urethral meatus on the vaginal wall. Biopsy showed squamous cell carcinoma, Grade IV. This was treated with 60 kv., 1 mm. Al filter, 6 cm. focus skin distance, 3 cm. cone to an air dose of 6,500 r in 17 days. On January 4, 1952 an ulcerated 4×3×3 cm. right inguinal metastatic lymph node was treated by a single plane radium implant for 7,000 r. This patient was last seen on May 5, 1961 without disease, 10 years after treatment of the vaginal metastasis.

Case E.H., a 70 year old white female, was referred on May 8, 1955 after a biopsy from

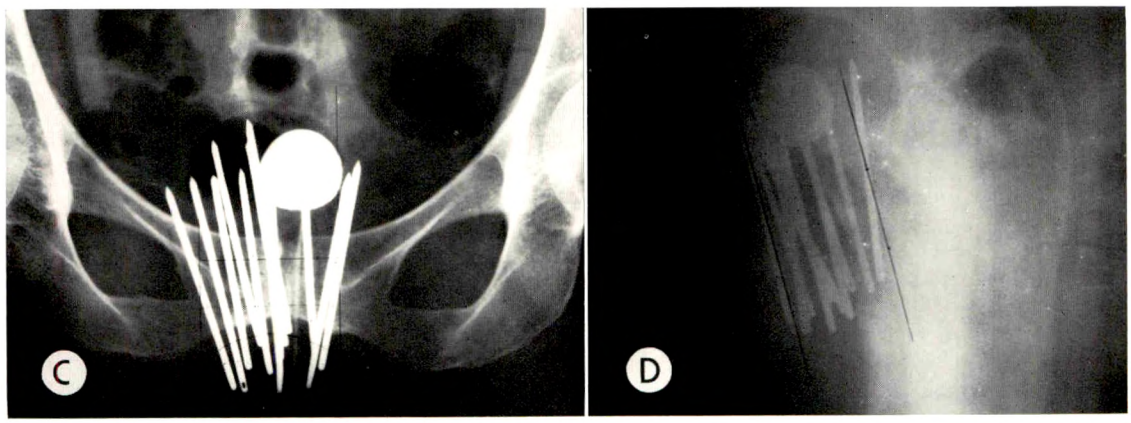


Fig. 3. (*C* and *D*) Volume radium implant used in Case M. W. of Figure 3, *A* and *B*.



Fig. 4. Case A. D., a 49 year old white female, was seen (*A*) on June 14, 1960, 2 weeks postoperatively for an incompletely resected squamous cell carcinoma of the distal urethra. On examination, there was infiltration around the clitoris. Biopsy showed squamous cell carcinoma at the clitoris and granulation tissue at the periurethral region.

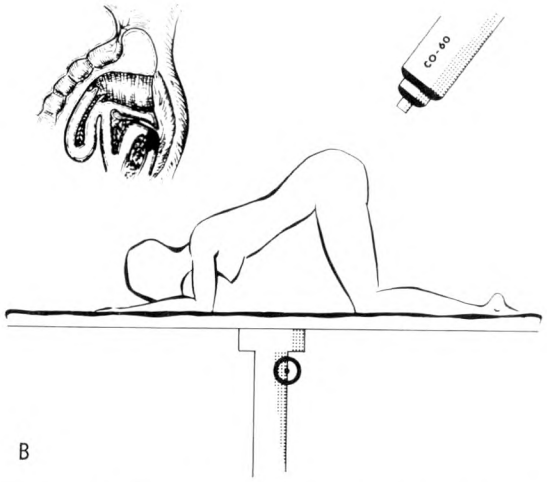


Fig. 4. (*B*) Case A. D. of Figure 4*A*. A minimum tumor dose of 6,050 rads, calculated at 3 cm. depth, was given in 5 weeks through a single 9×11 cm. perineal field with the patient in knee-chest position with the cobalt 60 unit. Supplemental treatment with 140 kv., 3 cm. cone for 1,000 rads in two treatments was given to the residual tumor on the clitoris. The patient was seen on June 5, 1961 with no evidence of tumor.

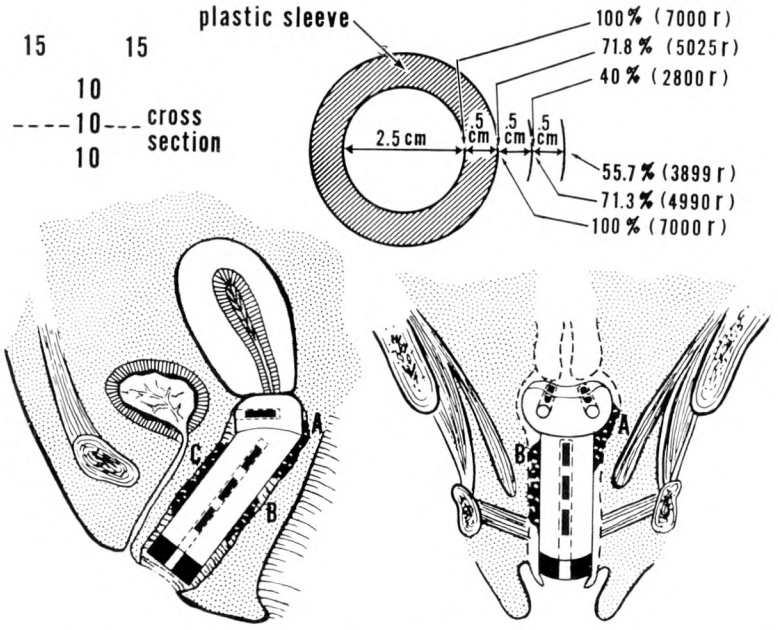


Fig. 5. Treatment plan for tumors on the posterior and lateral walls of the vagina.

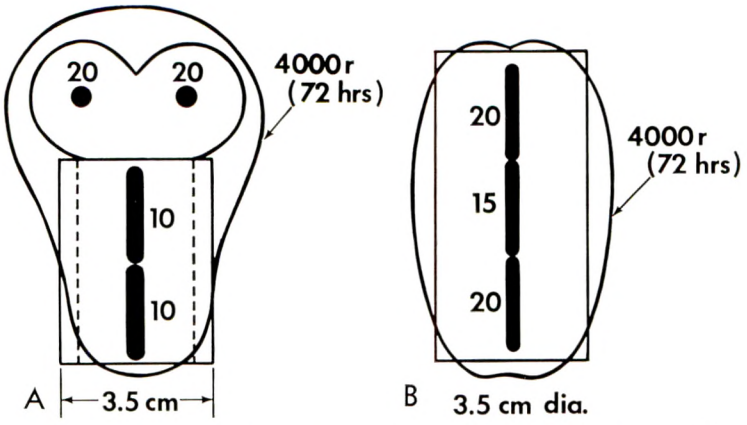


Fig. 6. Diagram showing the larger area of irradiation when (*A*) the Bloedorn applicator is used as compared to (*B*) the cylinder applicator.

the vagina revealed squamous cell carcinoma, Grade III. On examination, there was an indurated tumor involving the suburethral area and the right side of the introitus, extending upward to the clitoris and inferiorly to the posterior fourchette. The tumor involved the labia minora and was fixed anteriorly to the right pubic ramus and laterally to the ischium. The mass was estimated to be 3 cm. in depth, 5 cm. in width, and 6 cm. in length.

Treatment was administered through an 8×10 cm. anterior field with the 22 mev. betatron unit for 3,150 rads given dose and a cobalt 60 unit 9×7 cm. right perineal field for 5,700 rads given dose. The calculated tumor dose was 7,200 rads in $6\frac{1}{2}$ weeks.

Follow-up examination was uneventful except that several dilatations for stricture of the urethra had to be done. On February 25, 1960 she had had a total thyroidectomy for a papillary carcinoma of the thyroid gland. The patient was last seen on December 1, 1960 without disease, and was contacted on February 5, 1962 alive and well, 6 years after treatment.

Three other treated cases are shown in Figures 2, *A* and *B*; 3, *A–D*; and 4 *A*.

II. Tumors of the Lateral and Posterior Vaginal Walls

Lesions limited to the vaginal wall are effectively treated with intracavitary radium either in a cylinder or a Bloedorn applicator* (Fig. 5). A surface dose of 5,000 to 6,000 r is given in one insertion for shallow lesions and 7,000 to 9,000 r, fractionated, in two insertions in 10 to 14 days for thicker lesions.

The Bloedorn applicator provides a larger area of effective irradiation at the vault (Fig. 6). This applicator is preferred to a cylinder for lesions of the upper vagina in posthysterectomy patients. The fractionated insertions seem to preserve a better vaginal function by producing less fibrosis and obliteration of the vaginal canal. A cancerocidal dose to a selected depth should not be given if the mucosa receives a necrotizing dose.

Radium implants are used for tumors with moderate infiltration (Fig. 7). Implants alone or in combination with a vaginal applicator may be employed.

Illustrative Cases

Case A. G., a 74 year old white female, was admitted on November 12, 1956 with an adenocarcinoma of the endometrium. She was treated with the Hayman packing technique and a vaginal applicator. A surface dose of 7,000 r was given with the vaginal applicator which contained two 10 mg. radium sources in the ovoids and one 10 mg. source in the cylinder. A hysterectomy was performed 6 weeks later and the specimen showed many necrobiotic cells of adenocarcinoma in the endometrium, with foci of viable tumor; the lymph nodes were negative for cancer. One year later, in November, 1957, a metastasis developed on the right vaginal wall

* Designed by Fernando G. Bloedorn, M.D., formerly associated with this institution, now with the University of Maryland Hospital, Baltimore, Maryland. This applicator combines vaginal ovoid(s) and a vaginal cylinder.

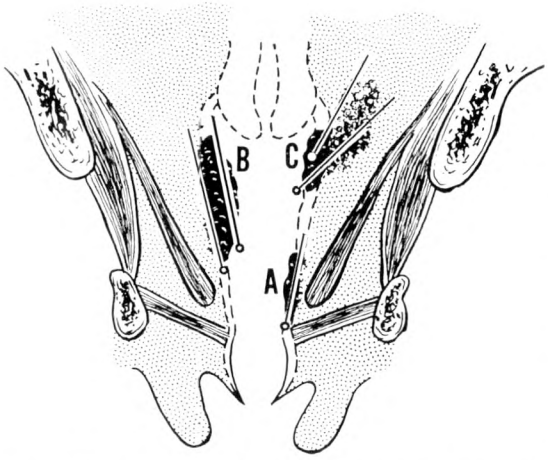


Fig. 7. Treatment plan for tumors on the lateral wall with moderate infiltration: A—single plane implant; B and C—two plane implants.

just below the margin of the previous vaginal radium source. The area was excised for biopsy and then given 7,000 r in 128 hours with a radium implant. The implant consisted of sixteen 2 mg., 4.5 cm. dumbbell needles. There was no recurrence on September 26, 1961, 4 years after treatment of the vaginal metastasis.

Case C. S., a 58 year old white female, was seen on January 15, 1955 with a large tumor over the upper posterior vaginal wall at the junction of the lower and middle third. There was extensive infiltration in the left paracolpos and parametrium to the pelvic wall. Infiltration was also noted extending to the right pelvic wall. Biopsy of the vaginal lesions showed squamous cell carcinoma; the cervix was negative on biopsy.

The patient was treated with the 22 mev. betatron unit using the whole pelvis radiation technique to 6,000 rads with an additional 1,000 rads to the left side of the pelvis with a reduced field. This was followed by a 72 hour insertion of a uterine tandem with 15-10-10-10 mg. radium sources and small ovoids, 12-12 mg. radium sources. A pelvic lymphadenectomy yielded lymph nodes negative for cancer.

This patient was followed and was without evidence of disease for 5 years. She died on February 16, 1960 from an intestinal obstruction with perforation resulting from an adhesion. No cancer was found at autopsy.

Two other cases are shown in Figures 8 and 9.

III. TUMORS LOCATED ON THE ANTERIOR VAGINAL WALL OR URETHRA

Tumors of the urethra or more advanced infiltrating tumors, primary or secondary, of the anterior vagina can be managed by a radium implant (Fig. 10, *A*, *B* and *C*) either alone or in combination with external irradiation. Because of the frequent extension of tumor in the bladder neck or trigone, an efficient implantation can be performed only with a special technique, using a suprapubic cystotomy.



Fig. 8. Case M. J., a 63 year old Negro female, was seen on December 28, 1954 after an outside diagnosis of carcinoma of the vagina had been made from a biopsy specimen. On the posterior vaginal wall, beginning approximately 2 cm. distal to the cervix, was a superficial papillomatous lesion, about 4×3 cm. in size and about 3 cm. thick. Biopsies of the cervix and endometrium were negative. The patient was treated with intracavitary radium for 56 hours with a Bloedorn applicator, using a 15 mg. source in a medium ovoid and three 20 mg. sources in the cylinder shaft, on January 14, 1955. The same treatment was repeated on January 28. The location of the lesion was shown by metal clips. A total dose of 9,000 r was delivered to the surface of the lesion. The patient also received 3,200 rads to the parametria using the 250 kv. unit. She was followed 6 years without evidence of disease.

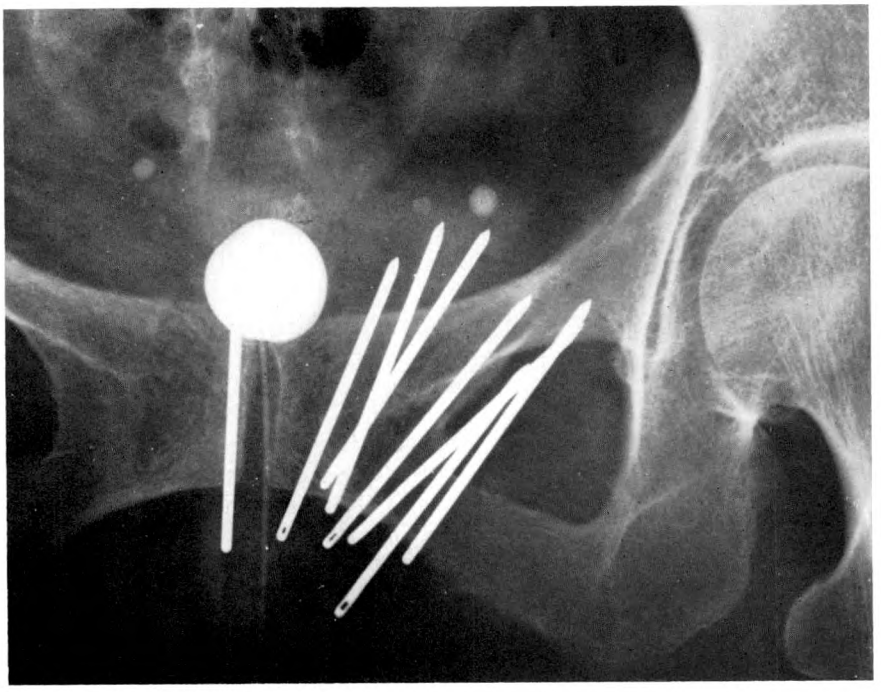


FIG. 9. Case R. F., a 56 year old white female, was referred on December 30, 1954, with a history of having had a hysterectomy for adenocarcinoma of the fundus uteri in 1948. In 1953 the patient noticed a tumor in the vagina which was observed by her doctor and removed in November, 1954. The specimen showed metastatic adenocarcinoma. On examination there was a 1 cm. ulcerative tumor at the middle third of the left lateral vaginal wall with extensive infiltration extending to the lower vagina and the left side of the rectovaginal septum. Rectovaginal examination showed paracolpal infiltration to the pelvic wall and a 4.5 cm. left paracolpal mass. A tumor dose of 3,000 rads to the left pelvis was given with the 22 mev. betatron unit in 5½ weeks. Following this, 4,000 r in 72 hours was delivered to the left upper vagina with a volume radium implant of eight 2 mg. 4.5 cm. dumbbell needles. She was well until September 8, 1959 when she developed pulmonary metastasis. She was last seen on August, 31, 1961, 6½ years after the initial treatment.

This technique has, in our experience, special merit in: (a) lesions involving the upper vaginovesical septum, (b) carcinoma of the posterior urethra, (c) tumors of the upper lateral wall with paracolpal extension, and (d) carcinoma of the cervical stump or vault recurrence.

The patient is draped in lithotomy posi-

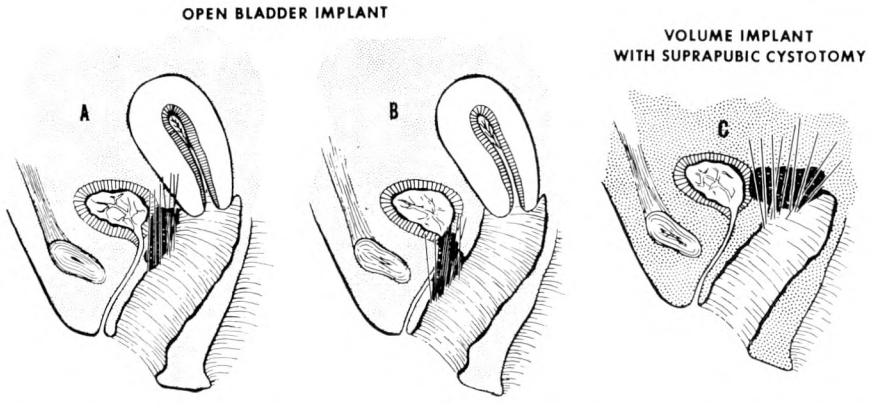


FIG. 10. Treatment plan for (*A* and *B*) anterior vaginal wall and (*C*) vault tumors.

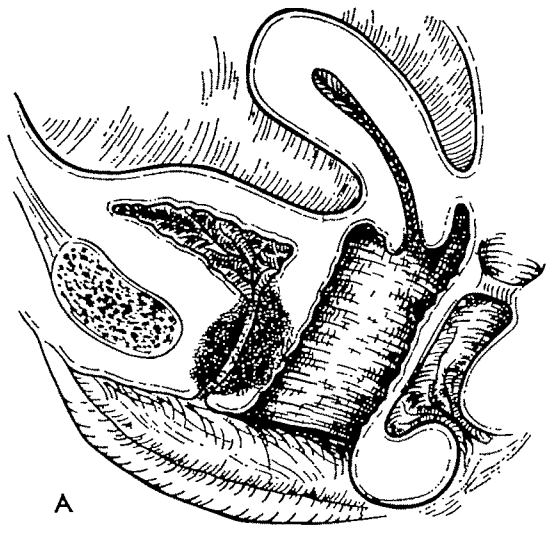


Fig. 11. Case F. G. (*A*) Diagram showing tumor mass in the posterior urethra and bladder neck.

tion and an extraperitoneal cystotomy is done. The operator can define, by direct palpation, the area of involvement—particularly the extension into the bladder trigone. The radium implantation is performed transvaginally with one hand, while the other hand, placed in the bladder, guides the course of the needles. This makes possible a precise transfixation of the involved bladder trigone and the implantation of paravesical masses by the radium needles.

ILLUSTRATIVE CASES

Case F. G., a 59 year old Negro female, was seen on September 22, 1960 with a 6×3 cm. tumor mass in the posterior urethra and the bladder neck (Fig. 11*A*). The lesion extended to within 1 cm. of the urethral meatus. Cystoscopy revealed tumor submucosally at the trigone. The pathology was squamous cell carcinoma. Four thousand rads in 4 weeks with the 4 field technique to the whole pelvis were given with the 22 mev. betatron unit. An open bladder implantation with iridium 192 needles in 2 planes was performed (Fig. 11, *B* and *C*), delivering 4,500 r in 50 hours. Follow-up was uneventful until December 15, 1961 when metastases in the upper abdomen and supraclavicular region were found. She was last seen on March 2, 1962.

Case P. T., a 77 year old white female, was seen on August 7, 1958 with a superficial ulcerated lesion measuring 3.5×2.0 cm. at the junction of the middle and lower third of the anterior and right lateral vaginal walls. The biopsy showed anaplastic squamous cell carcinoma. The cervix was normal but biopsy by a sharp conization disclosed a small focus of carcinoma *in situ*. The conization was felt adequate and no further treatment of the cervix was considered necessary.

A radium implantation was done on August 19, 1958, delivering 7,000 r in 196 hours. Nine 2 mg. and two 3 mg. radium needles were used. A year later on September 2, 1959 a small squamous cell carcinoma was found in the cervix and was treated by intracavitary radium. The patient has been free of disease and was last seen on September 28, 1961, 3 years after the initial treatment.

IV. TUMORS OF THE VAULT

Metastases of adenocarcinoma of the fundus or squamous cell carcinoma of the cervix after hysterectomy are common at this site. Superficial tumors are treated with vaginal ovoids alone (Fig. 12, *A* and *B*) or in combination with a cylinder and/or 250 kv. cone therapy. For more infiltrative lesions, a radium implant with an open bladder technique is necessary. A primary vaginal cancer with the uterus in place is treated by uterine tandem and ovoids.

ILLUSTRATIVE CASES

Case D. T., a 60 year old white female, was seen with a large infiltrating tumor at the right vaginal fornix which extended anteriorly under the base of the bladder. The extension of the tumor was fixed anteriorly to the right pubic ramus. The cervix was not involved. Biopsy of the tumor showed squamous cell carcinoma, Grade III.

On March 23, 1953 an intrauterine tandem with 25-10 mg. radium sources and 15-15 mg. radium sources in the vaginal cylinder was applied for 91 hours. The vaginal applicator delivered a maximum surface dose of 9,600 r and a minimum of 7,300 r. On April 3, 1953 a radium implantation was performed together with the insertion of a 2 inch tandem with 11.6-5.8 mg. radium sources. The implant consisted of three 2 mg. dumbbell needles, four 1.5 mg. dumbbell

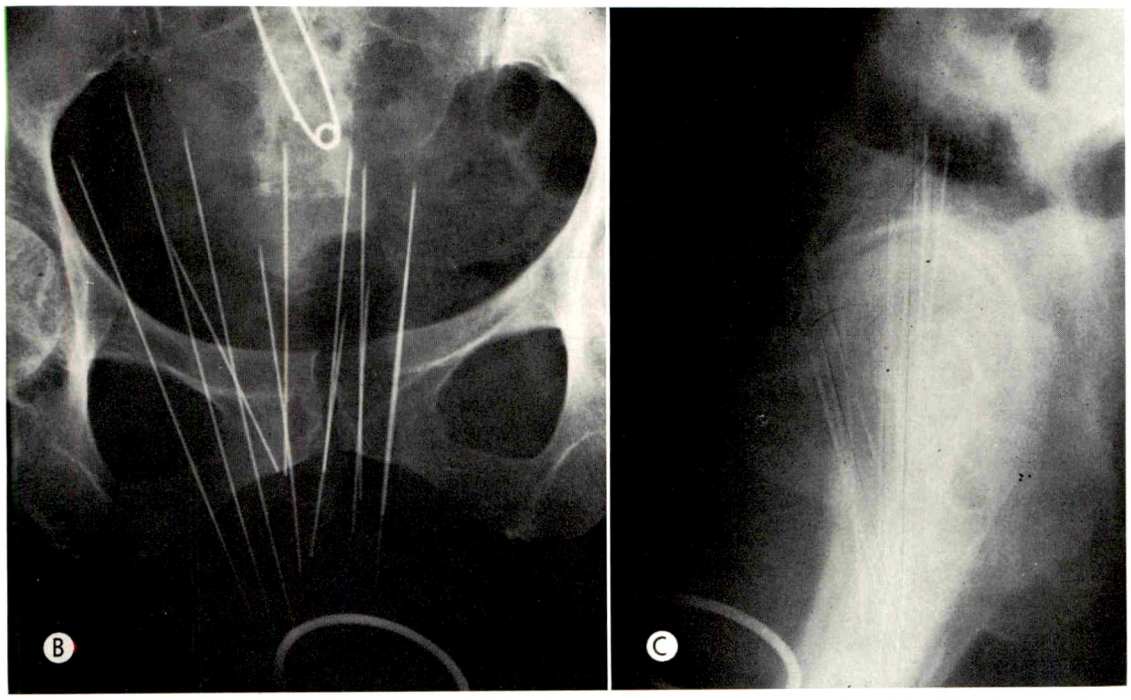


FIG. 11. Case F. G. (*B* and *C*) Treatment plan consisted of an open bladder implant with iridium 192 needles.

needles, three 2 mg. full intensity needles, and two 1.33 mg. full intensity needles for a total of 20.66 mg. for 96 hours. The tandem was removed after 76 hours. Two thousand five hundred rads were given to the right parametrium with the 400 kv. unit from March 30, 1953 to May 6, 1953.

The patient's recovery was uneventful. She was last seen on May 2, 1961, 8 years after treatment, with no evidence of disease.

CASE N. W., a 44 year old white female, was admitted on March 4, 1958 following a panhysterectomy on January 23, 1958 for an adeno-

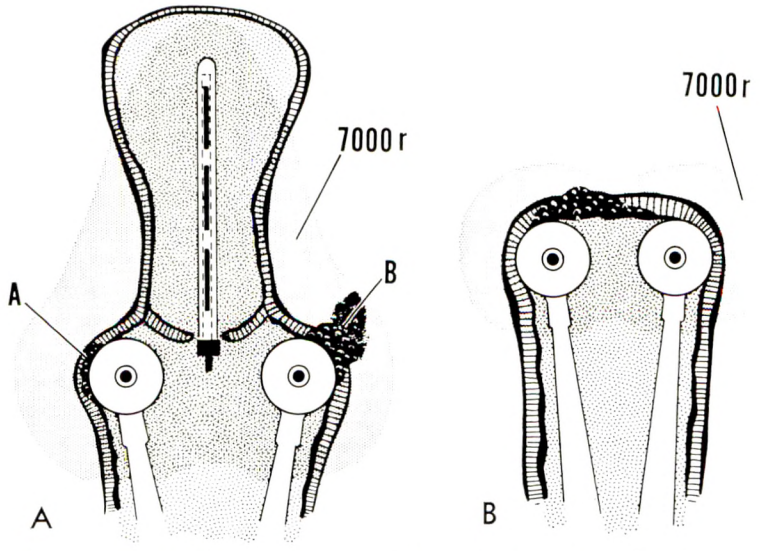


FIG. 12. (*A* and *B*) Treatment plan for superficial tumors of the vault using vaginal ovoids.

TABLE II

EXTENT OF DISEASE

ADVANCED SQUAMOUS CELL CARCINOMA OF VAGINA AND METASTASES FROM ADENOCARCINOMA OF FUNDUS

Total No. of Cases		Advanced Lesions*	Tumor Fixed to Pelvic Arch	Involved Vulva	Unilaterally to Pelvic Wall or Midpelvic Disease	To Both Pelvic Walls	Inguinal Metastasis
Squamous Cell Carcinoma of Vagina	36	18	2	2	7	3	4**
Metastasis from Adenocarcinoma of Fundus	18	6	0	0	6	0	0

* More than one extravaginal spread may be present while only one is listed.
** 2 patients with lesions too advanced for treatment.

carcinoma of the fundus which had extended to the cervix. Upon examination, the vaginal vault showed an area of granulation tissue with sutures. A biopsy obtained from the vaginal vault was reported as adenocarcinoma in the submucosa. There was induration from the vault extending to the left pelvic wall, thought to be representative of infiltrating tumor with post-surgical changes.

Treatment was started with 22 mev. betatron whole pelvis irradiation of 4,000 rads. The treatment fields were then reduced, delivering 7,000 rads in 7 weeks to the midline and left pelvic wall. A single medium ovoid with 20 mg. of radium was applied for 72 hours with a surface dose of 8,660 r. The patient was last seen, without disease, on August 10, 1961, $3\frac{1}{2}$ years after treatment.

Figure 13, *A* and *B* shows a case treated by radium implant.

RESULTS OF TREATMENT

The squamous cell carcinomas of the vagina and the metastases from adenocarcinomas of the fundus are classified into two clinical groups in order to correlate the results of treatment with the extent of the tumor.

A. *Limited Lesions*. The tumor is confined to the vaginal wall or there is only minimal perivaginal extension.

B. *Advanced Lesions*. There is gross extravaginal spread in either the paracolpal or parametrial region, extending to or fixed to the pelvic wall, or the tumor has extended outside the vagina into the vulva, bladder, rectum, or metastasized to the groins. These advanced tumors are shown in Table II. The 6 advanced cases of metastases from adenocarcinoma of the fundus had mid-pelvic extension or peripheral pelvic metastases.

I. SQUAMOUS CELL CARCINOMAS OF THE VAGINA

Of the 36 cases of primary untreated squamous cell carcinomas of the vagina, 10 had had hysterectomy for various reasons. The techniques of treatment for tumors of the vaginal vault were modified by the

TABLE III

RESULTS OF TREATMENT
SQUAMOUS CELL CARCINOMA OF VAGINA
LIMITED LESIONS

Total No. of Cases	18	
No Treatment	2	(dead 0 and 1 yr.)
Excision	1	(dead 3 yr., carcinoma of urinary bladder)
Irradiation	15	
Alive and well	10	(3 to 12 yr.)
Dead	5	
Recurrence	1	($2\frac{1}{2}$ yr.)
Other malignancy	1	(1 yr.)
Intercurrent disease	1	(2 yr.)
Distant metastases	2	(6 mo., 4 yr.)

Complications: Temporary necrosis (radium implant), 2 cases; vesicovaginal fistula (after radical vulvectomy for recurrence), 1 case; and temporary vesico- and rectovaginal fistula (tandem and ovoids), 1 case.

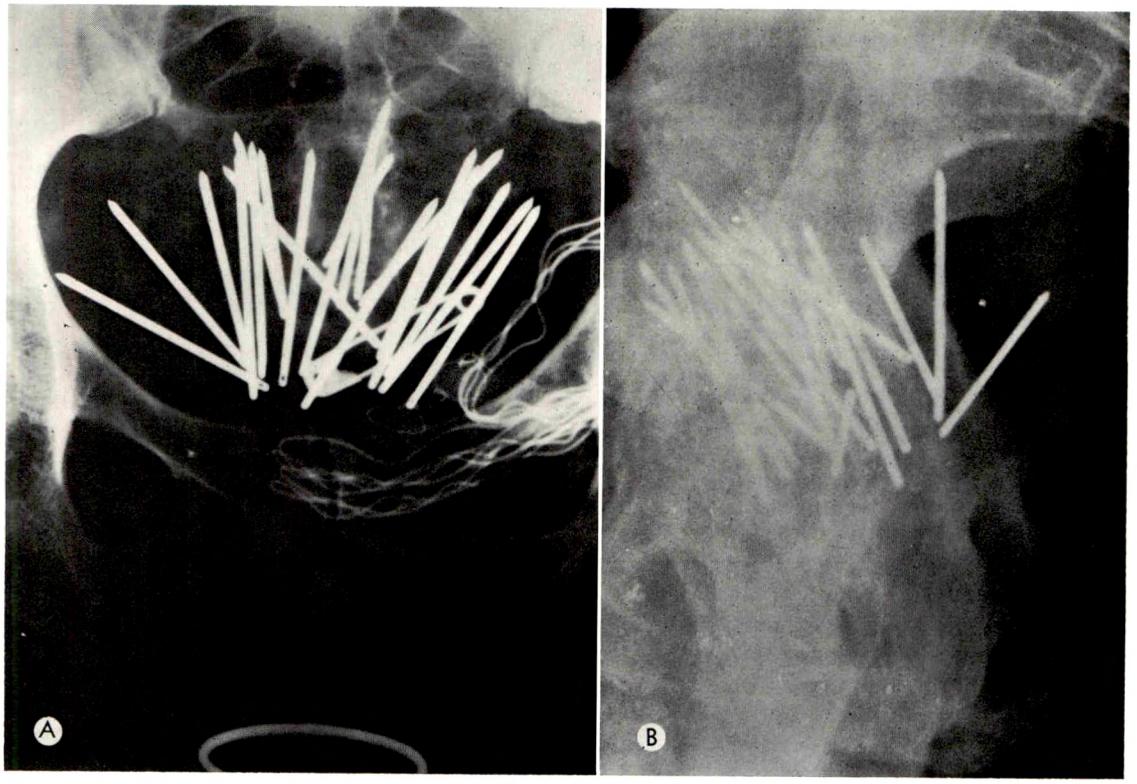


Fig. 13. Case A. R., a 39 year old white female, had a hysterectomy 2 years previously for squamous cell carcinoma of the cervix. Surgery was followed by external irradiation with approximately 2,000 rads tumor dose. She was first seen in this institution in January, 1954. There was granular recurrence on the vault of the vagina as well as extensive involvement of the base of the bladder which was detected by cystoscopy. Both the vaginal and bladder recurrences were positive for cancer by biopsy. (*A* and *B*) A radium implant of the vault and base of the bladder through the vagina with an open bladder (suprapubic cystotomy) was performed on February 12, 1954. Because of invasion of the left parametrium, an extra plane of needles was placed there. A tumor dose of 7,000 r was delivered. Following this implant, a tumor dose of 4,000 rads was given in 26 days to the lateral aspects of the parametria and the pelvic walls with a cobalt 60 unit. Central shielding and a wedge filter were used. The patient had an uneventful recovery. The vault healed rapidly. During the first 2 or 3 years, a shallow ulceration and small calculi were noted on the base of the bladder. During the last several years cystoscopies had been negative except for telangiectasia. The patient was last seen in January, 1962. The vault was soft and there was very little pelvic fibrosis.

absence of the uterus. There was, however, no apparent difference in the results obtained in these patients.

The survival time of these patients is given in Table III and Table IV according to the extent of the disease. Sites of disease, modalities of treatment and results are presented in Table V and Table VI.

The irradiation treatment for the early and limited lesions was very effective irrespective of the sites of the tumors. Control of the primary lesion was obtained in 82 per cent of the 15 early cases with only 2 irradiation failures. Parametrial irradiation

Table IV

RESULTS OF TREATMENT
SQUAMOUS CELL CARCINOMA OF VAGINA
ADVANCED LESIONS

Total No. of Cases		18
No Treatment (too advanced)		2
Irradiation		16
Alive and well		3 (5, 6 and 8 yr.)
Dead		13
Recurrence	8 (5 mo. to 3 yr.)	
Intercurrent disease	2 (4 yr., 22 mo.)	
No data	3 (2 at 1 yr., 1 at 3 mo.)	

Complications: Necrosis from radium implant in re-treating recurrence; and multiple fistulae (7,000 rads total pelvis and exenteration).

TABLE V

SITES AND TREATMENTS

SQUAMOUS CELL CARCINOMA OF VAGINA—LIMITED LESIONS

No.	Site	Basic Treatment	Supplementary Therapy	Results
1	Vault	Tandem and ovoids 2×72 hr.	400 kv., 2,000 rads, parametrial irradiation	Well at 12 years
2	Vault	Tandem and ovoids 48 and 72 hr.	400 kv., 2,000 rads, parametrial irradiation	Recurrence in 5 mo.; surgery; dead at 2½ yr.; local recurrence
3	Vault	Ovoids 72 and 48 hr.	400 kv., 5,000 rads, parametrial irradiation	Dead at 1 yr.; carcinoma of ovary
4	Vault	Bloedorn applicator 10,000 r	22 mev., 1,450 rads	Dead at 6 mo.; lung metastasis; vagina free of disease
5	Vault	Ovoids 60 and 40 hr.		Dead at 2 yr.; heart disease
6	Vault	22 mev., 5,000 rads; Bloedorn applicator 3,000 r		Recurrence in 2½ yr.; exenteration; dead at 4 yr.; distant metastases
7	Lateral wall	250 kv. transvaginal 2,500 rads; single plane implant 5,000 r; ovoid 72 hr.		Well 3½ yr.
8	Lateral wall	Tandem and ovoid, 2×40 hr.; single plane implant (not calculated)	400 kv., 3,000 rads, parametrial irradiation to right pelvis	Well 9 yr.
9	Lateral wall	Tandem 96 hr., Bloedorn applicator 8,000 r		Well 3 yr.
10	Lateral wall	Single plane implant 7,000 r		Local necrosis for 2 yr.; well 4 yr.
11	Anterior wall	Single plane implant 7,000 r		Well 3 yr.
12	Anterior wall (entire)	22 mev., 3,800 rads; Bloedorn applicator 4,000 r		Well 4 yr.
13	Posterior wall	Bloedorn applicator 9,000 r	250 kv., 3,200 rads, parametrial irradiation	Well 6 yr.
14	Posterior wall	Tandem and ovoids 2×72 hr.	400 kv., 3,000 rads, parametrial irradiation	Well 10 yr.
15	Introitus	Two plane implant 7,750 r; ovoids 48 hr.		Temporary necrosis for 5 mo.; well 3 yr.

Irradiation failures in 2 patients.

TABLE VI

SITES AND TREATMENTS

SQUAMOUS CELL CARCINOMA OF VAGINA—ADVANCED LESIONS

No.	Site	Basic Treatment	Supplemental Therapy	Results
1	Vault	Tandem 91 hr.; Bloedorn applicator 7,300 r; implant not calculated	400 kv., 2,500 rads to right pelvic wall	Well 8 yr.
2	Vault	22 mev., 7,000 rads, whole pelvis irradiation; single ovoid 48 hr.		Dead 5 mo.; recurrence
3	Vault	22 mev., 3,000 rads; open bladder implant 5,400 r; Bloedorn applicator 4,000 r	Lymphadenectomy (negative)	Well 5 yr.
4	Lateral wall	250 kv., 1,000 rads; ovoids 72 hr.; cylinder 7,600 r	400 kv., 2,700 rads to right pelvic wall	Dead 9 mo.; persistent carcinoma
5	Lateral wall	Cobalt 60 rotation; minimum 6,000 rads, maximum 7,800 rads in 5½ wk.	Lymphadenectomy (negative)	Radium implant for vaginal recurrence in 9 mo.; dead at 3 yr.; recurrence
6	Anterior wall	22 mev., 6,400 rads in 5 wk.; cobalt 60, 5,000 rads to right inguinal metastasis		No follow-up; dead at 3 mo.; no data
7	Anterior wall	22 mev., 5,000 rads in 5 wk.; volume implant 4,000 r; ovoids 67 hr.	Bilateral ilio-inguinal dissection (negative)	Dead at 2 yr.; recurrence
8	Anterior wall	Single ovoid 96 hr. (for palliation)		Dead at 2 yr.; persistent carcinoma
9	Posterior wall	22 mev., 7,000 rads, whole pelvic irradiation	Pelvic exenteration (no tumor)	Multiple fistulas; dead 1¾ yr.; no data; ? free of carcinoma
10	Posterior wall	22 mev., 6,000 rads, whole pelvic irradiation; 7,000 rads to left pelvic wall	Tandem and ovoids 72 hr.	Dead at 4 yr.; intercurrent disease; no carcinoma
11	Posterior wall	400 kv., 3,000 rads; 100 kv. transvaginal, 3,000 rads; Bloedorn applicator 4,000 r	400 kv. parametrial irradiation; 3,750 rads to right pelvic wall; 2,750 rads to left pelvic wall	Dead at 22 mo.; coronary
12	Posterior wall	400 kv., 4,200 rads; 2 plane implant 7,000 r	3,700 rads to pelvic wall	Dead at 9 mo.; recurrence

(*Continued on next page*)

TABLE VI (*Continued*)

No.	Site	Basic Treatment	Supplemental Therapy	Results
13	Posterior wall	250 kv., 3,800 rads to midline; 4,500 rads to pelvic wall; 2 plane implant 4,000 r		No evidence of disease on follow-up; dead at 1 yr.; no data
14	Introitus	400 kv., 6,000 rads in 6 wk.; 200 kv. transvaginal, 3,500 rads; single plane implant 3,000 r		Dead at 9 mo.; recurrence
15	Introitus	Cobalt 60 and 22 mev., 7,200 rads in 6½ wk.		Well 6 yr.
16	Introitus	2 plane implant 7,650 r; 250 kv., 3,000 rads to right pelvic wall	Surgery; metastasis to upper rectovaginal septum; cul-de-sac found nonresectable	Dead at 1 yr.; persistent carcinoma

Irradiation failures in 10 patients.

was given to 6 patients. Though its exact effectiveness was not clearly appreciated, it is felt that infiltrative lesions should receive parametrial irradiation for possible lymphatic extensions. Among the 16 late cases which were treated, irradiation failures were noted in 10 cases, rendering a control of the primary lesion by irradiation of approximately 37 per cent (6 cases).

TABLE VII

RESULTS OF TREATMENT

METASTASES FROM ADENOCARCINOMA OF FUNDUS

Limited Lesions	
Total No. Treated	12
Alive and well	4 (11, 10 yr., 2 at 4 yr.)
Dead	8
Vaginal recurrence	6 (6 mo., 2 at 1½ yr., 3½ yr., 4 yr., 8½ yr.)
Pelvic metastasis	1 (1 yr.)
Distant metastasis	1 (1½ yr.)
Irradiation failures	6
Advanced Lesions	
Total No. Treated	6
Alive and well	2 (3 yr., 6½ yr. with distant metastases)
Dead	4
Recurrence	3 (21, 11, 6 mo.)
No data	1 (1 yr.)
Irradiation failures	4

II. METASTASES FROM ADENOCARCINOMA OF THE FUNDUS

The survival time of 12 patients with limited lesions and of 6 with advanced lesions is given in Table VII. Table VIII and Table IX show the sites of these lesions and the mode of treatment of these patients. Local recurrences after treatment were frequent even in the limited lesions as only about 50 per cent of these were controlled. Most deaths resulted from pelvic recurrence or metastases. Death in the patients with advanced lesions usually occurred within one year.

III. CARCINOMA OF THE URETHRA

Table X is a classification of the cases of carcinoma of the female urethra according to site treated and extent of the tumor. This classification offers a better basis for comparison of the results than reporting by methods of treatment because in the latter the location and extent of the disease are not taken into consideration.

The results of treatment of the anterior urethral lesions without involvement of the

TABLE VIII

SITES AND TREATMENTS

METASTASES FROM ADENOCARCINOMA OF FUNDUS—LIMITED LESIONS

No.	Site	Months since Hysterectomy	Basic Treatment	Supplementary Therapy	Results
1	Vault	9	Ovoids 3,500 r; cylinder 3,500 r		Well 10 yr.
2	Vault	3	140 kv. transvaginal, 5,900 rads		Dead at 6 mo.; recurrence
3	Vault	25	Open bladder volume implant 5,500 r		Dead at 1½ yr.; abdominal carcinomatosis; ? vaginal recurrence
4	Vault	25	140 kv. transvaginal, 3,500 rads; cylinder 8,000 r		Dead at 1 yr.; pelvic lymph node metastasis
5	Vault	10	Cobalt 60 rotation, 6,100 rads; cylinder 7,000 r		Dead at 1½ yr.; distant metastasis
6	Vault	24	Single plane implant in 5 da. (not calculated); single ovoid 4,000 r; cylinder 3,000 r	Recurrence at vault at 1 yr.; radium implant 3,500 r; later, radium implant 6,000 r for bilateral groin metastasis	Dead at 4 yr.; recurrence
7	Vault	10	Ovoid 72 hr.; cylinder 24 hr.		Well 11 yr.
8	Lateral wall	12	Single plane implant 7,000 r		Well 4 yr.
9	Introitus	33	Bloedorn applicator 5,700 r	Recurrence 1½ yr. at suburethra; 2 plane implant 6,000 r; recurrence at vault 3 yr. from initial treatment; vaginectomy	Dead at 8½ yr.; recurrence
10	Introitus	13	2 plane implant 7,000 r	Exenteration 2 yr.; later for recurrence in entire vagina	Dead at 3½ yr.; recurrence
11	Introitus	9	60 kv. cone 5,750 rads	Diffuse pelvic metastasis at 2 mo.; later 140 kv. transvaginal 5,000 rads to vault; later volume implant 5,000 r for palliation	Dead at 1½ yr.; recurrence
12	Introitus	17	22 mev. 2,100 rads; Bloedorn applicator 5,000 r		Well 4 yr.

Irradiation failures in 6 patients.

TABLE IX

SITES AND TREATMENTS

METASTASES FROM ADENOCARCINOMA OF FUNDUS—ADVANCED LESIONS

No.	Site	Months since Hysterectomy	Basic Treatment	Supplementary Therapy	Results
1	Vault	2	22 mev. 4,000 rads to whole pelvis with 7,000 rads to midline and left pelvic wall; single ovoid 72 hr.		Well 3 yr.
2	Vault	27	250 kv. 3,000 rads; single ovoid 72 hr. (palliative)		Dead at 21 mo.; recurrence
3	Vault	13	22 mev. 6,000 rads to whole pelvis in 6 wk.; single ovoid 72 hr.		Seen at 10 mo. with no evidence of disease; dead 1 yr.; no data
4	Vault	12	Bloedorn applicator 7,000 r	Laparotomy; inoperable mass at vault; pelvic lymph node metastasis	Dead 11 mo.; recurrence
5	Anterior wall	24	Cobalt 60 rotation; 7,400 rads to midline, 5,200 rads to pelvic wall		Dead at 6 mo.; pelvic mass
6	Lateral wall	72	22 mev and coblat 60, 6,000 rads to left pelvic wall; volume implant 4,000 r		Living $6\frac{1}{2}$ yr. with lung metastasis

Irradiation failures in 4 patients.

vulva were very satisfactory. Radium implants either by volume or 2 planes proved equally effective (Table XI). Poor control of the primary was noted when the tumors involved the vulva (Table XI).

The treatment and clinical courses of 5 patients with posterior urethral tumors are shown in Table XII. Only 2 patients were salvaged.

Radium implants alone or combined with 4,000 rads delivered with external irradiation yielded poor results in cases of tumors of the entire urethra. All patients died from local recurrences (Table XIII). Control of the urethral tumor was obtained in 2 patients who were treated with 6,000 rads external irradiation and followed by a radium implant delivering 3,500 r.

In lesions of the posterior urethra or entire urethra, involvement of the neck and trigone of the bladder was common and recurrences were frequently found in these areas. High dose supervoltage external irradiation of 6,000 rads alone or supplemented with smaller dose given with a radium implant has shown encouraging results. Better control is obtained with supervoltage than with orthovoltage therapy, but more cases are needed before a definite conclusion can be reached.

Surgical resection for recurrence was performed in 3 cases after the initial treatment. Only 1 patient was salvaged.

IV. CARCINOMA IN SITU OF THE VAGINA

The treatment and results of 6 cases of squamous cell carcinoma *in situ* of the vagina are given in Table XIV. One case presented a new *in situ* carcinoma in another level of the vaginal sheath following initial treatment. Therapy was effective and without complications.

SUMMARY

Various types of malignant tumors of the vagina, justifying radical radiotherapy, have been discussed with reference to their histology, site of origin, and characteristics of spread.

The specific radiotherapeutic techniques for the various lesions of the vagina according to site have been described. The method of treatment is dictated by the site and extent of the disease irrespective of the his-

TABLE X

CARCINOMA OF THE FEMALE URETHRA

DISTRIBUTION ACCORDING TO SITE OF ORIGIN*

(Patients Seen 1950–1960)

Classification	No. of Patients	
Anterior urethra (perimeatal or submeatal)		12
(A) without involvement of vulva	9	
(B) with involvement of vulva	3	
Posterior urethra		5
Entire urethra		4
Entire urethra with regional metastases		4

* CHAU, P. M., and GREEN, A. E., JR.[2]

(*For Tables xii-xiv, please turn to following pages*)

TABLE XI

RESULTS OF TREATMENT

CARCINOMA OF THE FEMALE URETHRA—ANTERIOR URETHRAL LESIONS

(Patients Seen 1950–1960)

No. of Patients	Treatment	Clinical Evolution	Present Status
Without Involvement of the Vulva			
9	Radium implant two plane 6 volume 3	Uneventful	Living, no disease over 5 yr. 5 3 yr. 2 1 yr. 2*
With Involvement of the Vulva			
1	Volume radium implant, 6,500 r and bilateral groin dissection	Recurrence at 10 mo. and anterior exenteration	Dead at 2½ yr.; recurrence
1	250 kv., 5,000 rads in 5½ wk.	Recurrence on vulva at 8 mo.	Dead at 22 mo.
1	Cobalt 60, 6,000 rads in 5 wk. and additional 1,000 rads, 140 kv.	Uneventful	Alive and well 1 yr.

* One adenocarcinoma case had local recurrence at 8 months and was treated by anterior exenteration.

TABLE XII

RESULTS OF TREATMENT

CARCINOMA OF THE FEMALE URETHRA—POSTERIOR URETHRAL LESIONS*

(Patients Seen 1950–1960)

No. of Patients	Treatment	Clinical Evolution	Present Status
1	Volume radium implant, open bladder technique, 7,500 r in 80 hr.	Recurrence at bladder neck at 9 mo.	Dead at 1 yr.
2	Betatron 4,000 rads in 4 wk. and (A) 2,000 r radium implant	Recurrence at bladder neck at 6 mo.	Dead at 18 mo.
	(B) Iridium implant 4,000 r	Uneventful	Alive and well 1 yr.
2	(A) Betatron 6,000 rads 3 wk.	Radionecrosis of vagina and pubis	Alive and well 6 yr.
	(B) Betatron and cobalt 60 palliation, 4,600 rads in 5½ wk.	Persistent carcinoma	Dead at 2 mo.

* CHAU, P. M., and GREEN, A. E., JR.[2]

TABLE XIII

RESULTS OF TREATMENT

CARCINOMA OF FEMALE URETHRA—LESIONS OF ENTIRE URETHRA*

(Patients Seen 1950–1960)

No. of Patients	Treatment	Clinical Evolution	Present Status
Without Regional Metastases			
2	Volume radium implants 7,000 and 7,650 r in 4 and 6 da.	(A) Persistent tumor (B) Recurrence at 10 mo.; radical surgery	Dead at 8 mo. Dead at 2 yr.†
2	Betatron 6,000 rads in 6 wk. and volume radium implant 3,500 r	(A) Uneventful (B) Vesicovaginal fistula; radionecrosis of pubis and anterior vagina	Alive and well at 4 yr. Alive 2 yr. with pulmonary metastases
With Regional Metastases			
2	Betatron 4,000 rads and radium implant 5,000 r	(A) Recurrence at bladder neck at 8 mo. (B) Persistent carcinoma	Dead at 1 yr. Dead at 8 mo.
2	Betatron 7,000 rads in 7 wk., whole pelvis irradiation	(A) Persistent carcinoma (B) Peritoneal metastasis at 3 mo.	Dead at 8 mo. Living 1 yr. with metastasis

* CHAU, P. M., and GREEN, A. E., JR.[2]
† Pelvic lymph node recurrence.

TABLE XIV

RESULTS OF TREATMENT IN SITU SQUAMOUS CELL CARCINOMA OF THE VAGINA

No. of Cases	Treatment	Alive and Well
6	4 : Bloedorn applicator (4,000 r to 8,000 r)	3–4 yr.
	1 : 6,000 rads 60 kv. transvaginal cone	7* yr.
	1 : Total vaginectomy	1 yr.

* Initial lesion was at lower vagina. Vaginectomy 1 year later for vault *in situ* carcinoma.

tologic origin of these tumors. The results of treatment are given in each category.

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PRIMARY OVARIAN CANCER

A TWENTY-FIVE YEAR REPORT*

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THE interaction of many factors that may influence the prognosis for ovarian carcinoma makes it difficult to interpret the results of treatment procedures that have been utilized for the past 25 to 30 years. In an effort to understand more clearly the problems involved in the interpretation of results of therapy, and to apply the experiences of the past in the selection of treatment in the future, the data for patients with ovarian cancer treated during a 25 year period at the Hospital of the University of Pennsylvania were examined. The results of this study are reported herewith.

MATERIAL

The diagnosis of primary cancer of the ovary was recorded for 342 patients between January 1, 1935 and December 31, 1959. Excluded from this study are 57 cases in which the diagnosis had been made and initial therapy undertaken at another hospital, 7 cases in which it was doubtful that the cancer originated in the ovary, 1 patient who was dead on arrival at the hospital, and 2 cases in which the pathologic classification was adenoacanthoma arising in endometriosis of the ovary. The latter diagnosis has been excluded from the category of primary ovarian cancer; parenthetically, both patients are living without evidence of carcinoma, one 6 years and one 4 years after diagnosis. This report pertains to the remaining 275 patients, who were primarily diagnosed and treated in this institution.

In 1962, only 2 patients had been lost to follow-up sooner than 10 years after diagnosis; both of these were followed more than 5 years. All survival proportions in this paper are calculated by the life-table method.[3,8] Survival is measured from the date of first histologic confirmation of the disease.

RESULTS AND COMMENT

For the entire series, the 5 year survival was 41 ± 3 per cent* and the 10 year survival 36 ± 3 per cent.*

The distribution and 5 year survival of patients according to race, age and parity are given in Tables I–III. The age distribution is in accord with the findings of Dorn and Cutler[4] who showed that the incidence of ovarian cancer (adjusted for the distribution of ages in the general population) increases by a factor of 10 between ages 25–29 and 55–59, after which it decreases. The proportion surviving 5 years drops sharply with age, even after adjustment for the normal diminishing of life expectancy as age advances. It will be shown later that this is in part attributable to a greater relative incidence of the less favorable histologic types, and also of the more advanced stages, in the older patients. Table III shows a somewhat lower survival rate for the patients of parity higher than 2, but the absence of a gradient between para 0 and para 2 suggests that this is not a direct biologic relationship but is either a sampling error or else due to some associated variable, perhaps socioeconomic. Pregnancy occurred in association with the ovarian cancer in 5 patients, all of whom survived more than 5 years.

* Standard error.

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Presented at the Sixty-third Annual Meeting of the American Roentgen Ray Society, Washington, D. C., October 2–5, 1962. Some of these data were presented at the Eighth International Cancer Congress, Moscow, U.S.S.R., July 22–28, 1962.

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The incidence of previous, concurrent and subsequent malignancies originating at sites other than the ovary is reported in Table IV.

PATHOLOGY

There are many excellent histologic classifications of ovarian neoplasms, but unfortunately there is not sufficient conformity in the criteria for classification to make therapeutic reports from different sources directly comparable. Since the material in this report covers a 25 year period, it represents the opinions of several pathologists and also reflects some changes in thinking among pathologists. The Cancer Committee of the International Federation of Gynecology and Obstetrics met in Stockholm in 1961 for the purpose of proposing a standardized classification of the common epithelial ovarian tumors. They proposed separating each common tumor type into three categories: benign, possibly malignant, and obviously malignant. It was found to be impossible to classify the material from the University of Pennsylvania this way retrospectively, but the institutional record of benign ovarian conditions for the same time interval is presented in Table V, in order to show the proportion of cases in which malignancy was diagnosed.

In Table V, the serous tumors are shown divided into "papillary" and "simple" groups. Nearly half of the papillary serous tumors were malignant, while 95 per cent of the simple serous tumors were benign. This is in keeping with Taylor's[12] observation that papillary serous cystadenomas are more prone to malignant change than are simple serous cystadenomas.

It can be derived from Table V that over 80 per cent of all serous tumors diagnosed were classified as benign, a higher proportion than found in some other series.[6,12] Also, the survival rates for serous tumors, both papillary and nonpapillary, are high when contrasted with other reports.[5,7,12] These differences may be explained by the fact that at the Hospital of the University of Pennsylvania it has been customary to

TABLE I

RACE

Race	No. of Cases	5 Year Survival (per cent)
White	221	38
Non-white	54	53

TABLE II

AGE

Age (yr.)	No. of Cases	5 Year Survival (per cent)	
		Observed	Age-adjusted
10–19	3	67	67
20–29	12	75	76
30–39	39	64	65
40–49	66	45	47
50–59	86	30	32
60–69	55	32	37
70–79	13	14	21
80+	1	0	

Note: The age-adjusted survival rate is an estimate of the survival which would have been observed if no deaths had occurred except those due to ovarian cancer. The method is described by MacDonald[8] and the Middle Atlantic life tables[14] were used, with weighting for the observed racial distribution.

TABLE III

PARITY

Parity*	No. of Cases	5 Year Survival (per cent)
0	102	43
1	47	44
2	63	48
3–9	60	29

* In 3 case records, parity was not specified.

TABLE IV

PATIENTS WITH TWO CANCERS

Other Cancer	Breast	Uterus	Other Sites
Previous	5		4
Concurrent		5	2
Subsequent	1		7

TABLE V

OVARIAN PATHOLOGY: TOTAL INSTITUTIONAL EXPERIENCE, 1935–1959

Benign			Malignant			
	Patients			Patients		5 Year Survival
	(no.)	(per cent)		(no.)	(per cent)	(per cent)
			Pathology Group A			
			Dysgerminoma	1	0.4	100
Papillary serous cystadenoma	83	8.1	Papillary serous cystadenocarcinoma	66	24.0	64
			Granulosa cell tumor	17	6.2	59
			Pathology Group B			
Simple serous cystadenoma	352	34.3	Serous cystadenocarcinoma	19	6.9	57
Mucinous cystadenoma (5)	135	13.2	Mucinous cystadenocarcinoma	37	13.5	51
Benign teratoma	330	32.2	Malignant teratoma	10	3.6	40
			Papillary undifferentiated carcinoma	31	11.3	38
			Pathology Group C			
			Undifferentiated carcinoma	92	33.5	14
Fibroma (1)	87	8.5	Fibrosarcoma	1	0.4	0
Miscellaneous benign*	38	3.7	Gynandroblastoma	1	0.4	0
Total	1,025	100.0	Total	275	100.2	41
Endometriosis (7)	791		Adenoacanthoma	2		100
Non-neoplastic conditions and ovaries without pathology	6,336					

Note: The left side of the table represents the diagnoses from 8,152 patients whose ovaries were sent to the laboratory and a benign diagnosis registered during the period in which the cancer cases (right side of table) were collected. The numbers in parenthesis represent patients with two lesions; *i.e.*, who appear in another diagnostic category.

* Includes 15 Brenner tumors, 8 papillomas, 4 fibromyomas, 3 thecomas, 2 fibroadenomas, 2 arrhenoblastomas, 1 adenomyoma, 1 adenofibroma, 1 cystadenofibroma, and 1 cavernous hemangioma.

place all of the undifferentiated tumors in a separate category rather than to attempt classification of undifferentiated tumors as either serous or mucinous. Other investigators either do not establish a separate classification of "undifferentiated carcinoma" or "solid carcinoma"[6,10,11] or else find a very low incidence of such lesions,[1,12,13] in contrast to the relatively high proportion shown in Table v.

Ten histologic types (Table v) are represented in this series of cancer cases. The survival curve for each of these groups was plotted. Three general patterns of survival emerged. The groups with similar survival patterns were pooled and are shown in Figure 1.

A somewhat simpler correlation of histology and prognosis can be accomplished by ignoring the rare tumors and omitting

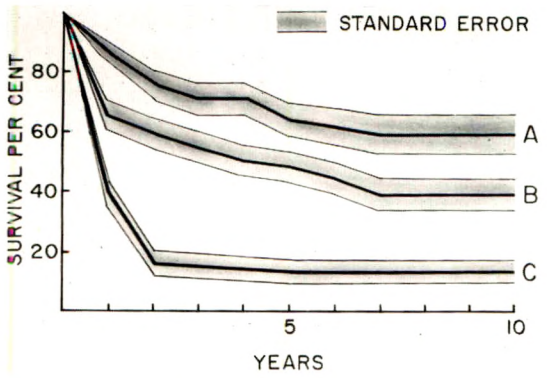


FIG. 1. Survival according to histologic type. The three curves represent the 3 pathologic groups defined in Table v.

the distinction between papillary and nonpapillary types. The result is a survival curve for serous tumors, a curve for mucinous tumors, and a curve for undifferentiated tumors closely resembling the three curves of Figure 1, but with somewhat larger standard errors that overlap in part of the range.

Table VI shows the distribution of the pathologic groups according to age. There was a greater proportion of the more favorable histologic types in the younger patients, which partially accounts for their better survival rate. However, there was a substantially better survival rate for the younger patients within each pathologic group as well.

STAGING

Laparotomy is essential for an effective clinical staging of ovarian cancer. In this series it was performed for every case even though the only objectives in a few of the cases were paracentesis and biopsy. Many reports have shown a high correlation between mortality and the extent of tumor found at exploration of the abdomen. In this report the cases were divided into the 5 categories shown in Table VII. Criteria for inclusion in the group with extension beyond the genital tract were: biopsied or grossly observed tumor beyond genital tract, ascites exceeding 300 cc., or pleural fluid. Table VII shows 3 separable survival patterns, which are confirmed by the curves plotted in Figure 2. Comparison of Figure 2 and Figure 1 suggests that clinical extent was an even better indication of prognosis than was histology. This is confirmed by Table VIII, which shows that prognosis

TABLE VII

EXTENT OF TUMOR AT TIME OF DIAGNOSIS

	No. of Cases	5 Year Survival (per cent)
Stage-Group I		
Tumor in only one ovary, removed intact	66	92
Stage-Group II		
Tumor in one ovary, ruptured or damaged in removal	37	69
Tumor in two ovaries	16	68
Other genital structures involved	13	54
Stage-Group III		
Extension beyond genital tract	143	6
	275	

TABLE VI

AGE, PATHOLOGY AND SURVIVAL

Pathology	Age Less Than 50			Age 50 or More		
	No. of Cases	Per Cent	5 Year Survival (per cent)	No. of Cases	Per Cent	5 Year Survival (per cent)
A	44	36.7	75	40	25.8	52
B	42	35.0	64	55	35.5	34
C	34	28.3	21	60	38.7	10
Total	120	100.0	55	155	100.0	30

* Pathology group as defined in Table v.

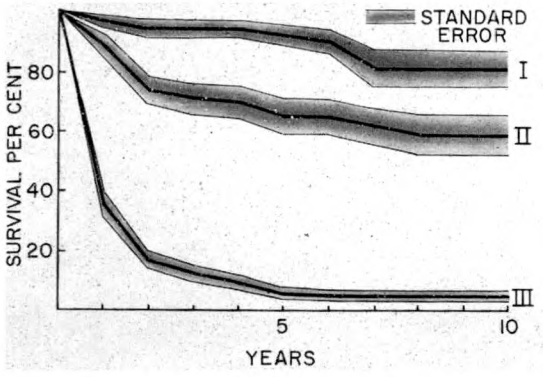


FIG. 2. Survival according to clinical stage. The 3 curves represent the 3 clinical stage-groups defined in Table VII.

varied much more with stage than with pathology. In addition, this table shows that stage and pathology are not independent; the intermediate and least favorable pathologic groups (B and C) contain a higher proportion of advanced stage patients.

Table IX shows that there was a greater proportion of early stage cases among the younger patients, but this still does not completely explain the better survival of the young, since it was better within each stage group as well.

SURGERY

There was a marked variation in the therapy programs utilized for the 275 patients, partly because of the 25 year span of time and partly because therapy was governed by the individual physician or chief of ward service. The first column of Table X shows that patients who had neither ovary removed very seldom survived 5 years, as might be expected. The second and third columns appear to show a small benefit of bilateral oophorectomy

TABLE VIII

STAGE, PATHOLOGY AND SURVIVAL

Stage-Group*	Pathology Group A**			Pathology Group B**			Pathology Group C**		
	No. of Cases	Per Cent	5 Year Survival (per cent)	No. of Cases	Per Cent	5 Year Survival (per cent)	No. of Cases	Per Cent	5 Year Survival (per cent)
I	28	33	92	29	30	93	9	10	89
II	29	35	86	24	25	58	13	14	38
III	27	32	17	44	45	10	72	77	0
Total	84	100	64	97	100	49	94	100	14

* Stage-Group as defined in Table VII.
** Pathology group as defined in Table V.

TABLE IX

AGE, STAGE AND SURVIVAL

Stage-Group*	Age Less Than 50			Age 50 or More		
	No. of Cases	Per Cent	5 Year Survival (per cent)	No. of Cases	Per Cent	5 Year Survival (per cent)
I	36	30.0	94	30	19.4	89
II	32	26.7	78	34	21.9	51
III	52	43.3	13	91	58.7	2
Total	120	100.0	55	155	100.0	30

* Stage-Group as defined in Table VII.

compared to unilateral, but the comparison is not entirely valid since the factors which determined the surgical choice in each case are not known now.

A hysterectomy was done in about two-thirds of the cases. Prior to 1950, supravaginal hysterectomy was frequently employed because it was then the most common uterine operation. After 1950 this procedure was generally reserved for patients in whom complete tumor removal was impossible. The first line of Table XI shows that when the whole series is examined, total hysterectomy appears to be associated with substantially better survival. However, when the series is divided by clinical stage, it is evident that there is a higher proportion of supravaginal hysterectomies in the most advanced category, which accounts for most of the apparent superiority of total hysterectomy.

RADIATION THERAPY

Nearly half of the patients were given postoperative irradiation as a part of the primary treatment plan. No uniform policy was employed in determining which patients would receive radiation therapy. The result is an interesting example of the difficulties of interpreting statistics. In Table XII, the first line shows that the patients who received no irradiation showed a striking superiority in survival rate. But the next three lines show that radiation therapy was used more often in the advanced cases, and within each of the arbitrary stage groups the difference in survival was not significant. In fact, the data are not rigidly incompatible with the hypothesis that irradiation improves survival rate. It is demonstrated with a crude staging system that irradiation was used most in the advanced cases. If a greater number of meaningful stage categories were possible, it is conceivable that irradiation might be associated with better survival in each, and still yield the over-all figures reported here.

The technique of postoperative radiation therapy, when it was used, varied considerably from patient to patient. This was in part due to changes in policy over the 25

TABLE XI

HYSTERECTOMY

	Supravaginal Hysterectomy / Total Hysterectomy	5 Year Survival	
		Supravaginal Hysterectomy (per cent)	Total Hysterectomy (per cent)
Whole Series	105/185	42	66
Stage-Group*			
I	24/56	92	91
II	27/56	59	75
III	54/73	10	7

* Stage-Group as defined in Table VII.

TABLE X

OOPHORECTOMY

Whole Series	No. of Cases / 5 Year Survival (per cent)		
	None 42/2	Unilateral 39/44	Bilateral 194/47
Stage-Group*			
I		16/100	50/90
II	1/0	8/63	57/70
III	41/2	15/0	87/9

* Stage-Group as defined in Table VII.

TABLE XII

POSTOPERATIVE RADIATION THERAPY

	Irradiated / Total Group	5 Year Survival (per cent)	
		Irradiated	No Irradiation
Whole Series	129/275	20	59
Stage-Group*			
I	9/66	89	93
II	23/66	57	69
III	97/143	5	7

* Stage-Group as defined in Table VII.

TABLE XIII

TECHNIQUE OF POSTOPERATIVE IRRADIATION IN STAGE-GROUP II PATIENTS

Central Axis Minimum Dose	Alive/Dead	
	Part of Abdomen	Whole Abdomen
roentgen-ray dose		
<1,500 rads	1/1	2/1
1,500–2,500 rads	2/2	1*/3
>2,500 rads	3/0	0/1
Au^{198} IP, >100 mc	4/2	

* Also given 100 mc Au^{198} intraperitoneally.

year period and in part to clinical individualization. It is evident from Table XII that intercomparison of techniques on the basis of survival rates will be uninformative in Stage-Group I, since nearly all patients survive, and in Stage-Group III since nearly all patients die. Only Stage-Group II is suitable for analysis of irradiation technique, and Table XIII shows no clear correlation between volume of tissue irradiated, total dose, or the use of colloidal radioactive gold.

SURVIVAL TIME

Treatment which fails to cure may be of value if it prolongs survival time. We found, as suggested by Boag,[2] that the cumulative percentage of nonsurvivors, plotted against the logarithm of months survived, approximated a straight line on probability paper (Fig. 3). To the extent that this is so, the logarithm of survival time may be considered to have a normal (Gaussian) distribution and logarithmic mean survival times may be statistically compared by the "t" test. In the largest stage-group, that with spread beyond the genital tract, the logarithmic mean survival time was 7.1 months for the patients who received postoperative irradiation and 3.6 months for those who did not, with a probability of less than 0.05 that the difference is due to sampling error. However, the proportion of deaths in the first 2 months is higher than indicated by the regression lines through the rest of the data. A certain number of the patients probably appeared to be beyond hope of salvage at time of diagnosis, and it is likely that the majority of these were not irradiated. If all surviving less than 2 months are excluded, the difference in survival time between irradiated and nonirradiated is not significant ($P>0.3$). In the groups with tumor confined to an ovary or to the genital tract, the difference was not significant.

Survival times were also compared for unilateral versus bilateral oophorectomy, total versus supravaginal hysterectomy, central axis radiation dose exceeding 2,500 rads versus lesser dosage, and irradiation of the whole abdomen versus irradiation of a part. No significant differences were found.

DATE OF TREATMENT

The trend in selection of therapy over the interval covered in this report has been in the direction of bigger operations and higher radiation dosage. It is of interest to observe in Table XIV that division of the report period into 3 equal intervals shows no significant alteration of the survival rate. The larger numbers of patients in the more recent intervals probably reflect increasing size and activity of the institution

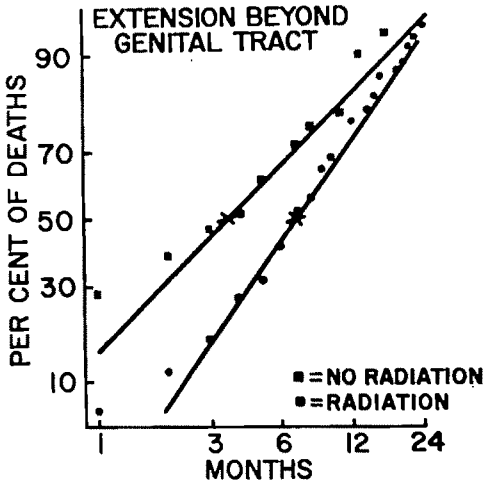


FIG. 3. Survival time and irradiation. The distribution of survival times for the Stage-Group III (cf. Table VII) patients, with and without postoperative radiation therapy.

rather than any change in the incidence of the disease. For comparison, the number of uterine corpus and invasive cervix cancers seen in the institution during these time periods is also given in Table XIV. The ratio of ovary to corpus cancer remained fairly constant at about 0.6. The number of invasive carcinomas of the cervix failed to show the increase seen in the other two sites, which may in part be attributed to the more frequent detection of cervix cancer in the noninvasive stage in recent years. Dorn and Cutler[4] found a 17 per cent increase in ovarian cancer incidence between 1937 and 1947, but pointed out that this might be due to better reporting.

Table XIV

CHANGES WITH TIME

Period	Ovary		Corpus	Cervix*
	Cases	5 Year Survival (per cent)	Cases	Cases
1935–1943	58	38	93	311
1943–1951	95	44	159	320
1951–1959	122	39	202	339

* Does not include noninvasive cervical cancers.

DISCUSSION

The principal purpose of compiling the results of treatment is to determine whether one treatment is superior to another so that the best treatment may be chosen for future patients. For this to be validly accomplished, two requirements must be met: (1) the series of cases must be representative of the cases which will be seen in the future; (2) the different treatments to be compared must have been applied to subgroups of patients which are comparable to each other, with respect to other variables which influence survival rate.

The first requirement would be met in part if the series could be shown to be a sample representative of the total world experience with the disease. Intercomparison with other series provides a test of this. Unfortunately, in the present instance such a comparison shows that the relative incidence of each type of ovarian neoplasm, and the proportion of each type which is considered malignant, varies considerably among reports. This suggests that the lack of uniformity in criteria for the diagnosis and classification of ovarian tumors may make it impossible to generalize the experience with treatment in one clinic to others, or even to future cases in the same institution.

The second requirement is even less well met in the material available here. It is evident that the different treatment subgroups are not comparable with respect to extent of disease. It may be inferred that the treatment selection for each patient was dependent upon many factors, of which some, such as the clinical stage, can crudely be extracted from the record but others, such as the attitude of the physician toward different forms of treatment, are inaccessible to retrospective study. These indefineable differences in the treatment subgroups make it dangerous to ascribe any observed differences in survival rate directly to the treatment.

It is difficult to escape the conclusion that the carefully kept records of a quarter of a century of experience in the treatment of ovarian cancer have very limited value in guiding treatment selection for future cases. The surgical and radiation therapies used were largely unsuccessful in the advanced cases but highly successful in the early cases. No one plan can be shown to be convincingly superior to another.

These data provide another example of the necessity for controlled studies in the evaluation of cancer therapy. One such study of ovarian cancer is in progress;[9] it is to be hoped that other carefully designed and rigidly controlled clinical trials will be organized to assess the relative merits of conventional treatments and of new therapeutic approaches as they are developed.

SUMMARY

1. The results of treatment of 275 patients with ovarian cancer at the Hospital

of the University of Pennsylvania, 1935–1959, are reported.

2. The factors which correlated most highly with survival were clinical extent of disease at time of diagnosis and histology. These two variables are not independent.

3. There was little correlation between survival rate and type of treatment employed, after allowance was taken of the extent of disease.

4. Controlled therapeutic trials, together with more uniform criteria for diagnosis and classification, are needed to better determine optimal therapy for ovarian cancer.

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The case records analyzed in this study and the follow-up information come from the Department of Obstetrics and Gynecology, F. L. Payne, M.D., Chairman, and the Department of Radiology, E. P. Pendergrass, M.D., Professor Emeritus. We are indebted to the Tabulating Department, directed by Mr. D. Drasen, for machine processing of the data.

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CURATIVE AIM AND RESULTS OF ROUTINE INTRAPERITONEAL RADIOCOLLOID ADMINISTRATION IN THE TREATMENT OF OVARIAN CANCER*

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THE author began intraperitoneal administration of radioactive colloids in 1945 and intrapleural administration in 1949. A few years later radioactive colloidal instillations were performed in other closed cavities, such as the pericardial and the subarachnoid space. The latter applications can still be considered as rather experimental.

Colloidal radioactive gold (Au^{198}) has remained hitherto the most suitable material for such treatments. Other radiocolloids such as chromic phosphate (P^{32}) and radioyttrium (Y^{90}), both pure beta emitters, are also increasingly used for intracavitary applications. Colloidal lutecium (Lu^{177}), as well as I^{131} combined colloidal oils, etc., have been studied recently by means of animal experimentation. At present internationally organized study groups and cooperative control of colloidal isotope preparations for medical use would be most useful and recommendable.

The intraperitoneal and intrapleural instillation of radioactive colloids is now widely accepted for palliative treatment of malignant effusions. Numerous published reports throughout the world confirm that useful, sometimes excellent, palliations can be obtained by this means in about 50 per cent of the cases.

Since these palliative results are so well known, it is the purpose of the author to be more specifically concerned with the possibilities offered by intracavitary radiocolloids for curative contributions in the field of cancer therapy. Having been in the position to gather extensive experience in the use of intraperitoneal radioactive gold in the treatment of ovarian cancer, including the so-called "good cases," a discussion of the available evidence for the use of radiocolloids as a curative measure will be given.

After having initiated the intraperitoneal injection of colloidal radiogold in association with artificial hydroperitoneum, such administrations were performed routinely by the author from 1949 on in all cases of ovarian cancer following, and very exceptionally preceding, surgery at the Women's Hospital, University of Zürich. This procedure was combined with conventional deep radiation therapy and included vaginal and, if possible, intrauterine radium. Such extensive use of intraperitoneal colloidal Au^{198}, often on an apparently "prophylactic" basis, seems logical, owing to the high incidence of early macroscopically invisible dissemination of tumor cells throughout the abdominal cavity, occurring in about 50 per cent of even the radically operated cases.

The present series of unselected patients, all having had intraperitoneal radiogold, has gained with time in scientific value, since statistically proved results are the sole decisive criterion of the clinical efficiency of any procedure employed in tumor therapy. For this reason, only the percentage of cures after 5 years will be considered.

Furthermore, since ionizing radiation, besides ablative surgery, is the only other means which has hitherto cured cancer, we have never accepted the suggestion of replacing the intraperitoneal colloidal Au^{198} with chemotherapeutic drugs, especially in

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Stage I and II cases, and even in Stage III cases. Additional chemotherapy with mustards and other agents may be given, however, in some incurable Stage IV cases.

A first account of the cures which were observed 5 years after such combined treatment in an unselected group of 51 ovarian cancer patients was presented at the *Second U. N. International Conference on the Peaceful Uses of Atomic Energy* (Document No. A/15/P/234), Geneva, 1958. The present publication is a continuation of this account but concerns now a substantially larger series of 118 patients treated at least 5 years ago. Surgery, as radical as feasible, is, of course, the primary procedure in this disease and was performed in most instances by the surgical team of our Hospital Unit, headed by Professor Held, although a number of cases had been operated elsewhere. All radiation treatments were given by the author, and autopsy findings on the deceased were available in practically all cases. A second publication including this same series of patients, *Radioactive Isotope Therapy, with Particular Emphasis on the Uses of Radiocolloids*, edited by the Division of Scientific Information of the *International Atomic Energy Agency*, 1962[10] is suggested for the especially interested reader who will find there many references as well as information on isotopic treatments in general. The present article is confined to the topic mentioned in the title.

METHOD

The method of intracavitary administration of radioactive colloidal gold is devised for efficiently combatting *early* serosal implants and lymphogenic metastases. As pointed out in the former publications, the soundness of the rationale is supported by the clinical results obtained, as well as by the physical radioassay of fairly homogeneous distribution and "paraselective" concentration of the intraperitoneally instilled colloidal gold. It is important to emphasize, in this respect, that experiments in animals and investigations in humans by means of radiocolloids in tracer doses are unreliable for the assessment of specific tissue radiation dosage, which becomes of increasing clinical significance. Hence, only studies made on human patients and on removed specimens, after isotope therapy at full clinical dosage can supply adequate and accurate information about the distribution of the particulate radioactive material in the organism, as well as about the radiation dosage thus realized and the corresponding radiobiologic effects.

The author's observations on autopsy material of a few patients with abdominal carcinomatosis, whose unrelated intercurrent death occurred about 1 to 2 weeks after the radiogold had been administered intraperitoneally, have established that secondary concentrations of the colloidal radioactive substance of a highly desirable type are indisputably present. Dosage assessments of the beta radiation based on autoradiograms and on neutron activation analysis, first employed by the author for precise medical dosimetric studies, show that after intraperitoneal administration of 150 mc of colloidal Au^{198},* diluted with about 400 ml. of physiologic saline (which corresponds to our standard technique), the following figures (extrapolated for full decay of the Au^{198}) are obtained: at least 4,000 rads for the peritoneal serosa, about 6,000 rads for the omentum, an average of 7,000 rads (with probable maxima up to 10,000–30,000 rads) for all the retroperitoneal and mesenteric, but also (and this is quite important) for the para-esophageal and paratracheal mediastinal lymph nodes. The actual "spilling" of the colloidal radiogold into the reticuloendothelial system of the liver and spleen accounts for only 170 rads and 250 rads, respectively, and, for the kidneys, about 30 rads, as shown by neutron activation analysis. About 750 rads of diffuse penetrating gamma radiation must be added, as we have estimated by calculation, for the intra-abdominal structures. Correspondingly high active deposits were also found after intrapleural administra-

* The specific activity of Au^{198} should be maintained at about 1 curie per gram of gold. Practically all these cases were treated with colloidal Au^{198} supplied by courtesy of the Isotope Division of the AERE, Harwell and Amersham, England.

tion within the pleural serosa and the mediastinal lymph nodes. Tumor cells, floating (and perhaps multiplying) in ascitic or pleural effusions or scattered around in early dry serosal disseminations, are then also submitted to a very efficient radiation bombardment.

These figures, quite reliable in their order of magnitude, are definitely of true practical significance since they are well within the range of therapeutically efficient radiation effects. It can thus be readily admitted from these dosimetric data and from clinical experience that such isotope therapy owing to this "paraselective" mode of distribution and concentration which follows the same pattern as the regional and systemic swarming of tumor cells and particles —leaving aside hematogenic generalization—is capable of destroying efficiently early serosal and lymphatic disseminations in even very extended areas. However, it is quite evident that, because of the limited range of the beta radiation, this "paraselective" action of radiogold therapy will be insufficient when the metastatic deposits have reached the advanced stages of gross node formations. Hence, intracavitary colloidal Au^{198} therapy does by no means replace conventional deep radiation therapy in its well established classic indications, but its essential advantage is to supply an efficient blockade and sterilization of the early stages of neoplastic microdisseminations, even when these have extended beyond the local and regional action range of the conventional procedures. In this respect, colloidal isotope administration should be considered a true progress (not a merely technical advance) in the field of radiation therapy.

As far as the technique of intraperitoneal and intrapleural administration of colloidal Au^{198} is concerned, many devices were developed for injecting the isotope material with minimal radiation hazard to personnel. Simple techniques are most suitable, since they allow a better reduction of the time required for the administration of the radiocolloid, which is the most important factor. If ascitic (or pleural) fluid is already present, it must first be withdrawn, leaving only enough (several hundred milliliters) for the final dilution of the colloidal gold, given with some added saline. This procedure is easy to perform. In cases without previous effusion, *i.e.*, almost all the cases with operable primary lesions (Stage I, II and III, see below), a very careful administration is mandatory, since the radioactive material must then be administered intraperitoneally in association with an artificial hydroperitoneum of 350–400 ml. In our experience of about 15 years, we have found that the best way to proceed is to do paracentesis by means of a rather thin special trocar with a horizontal supporting part, adjustable for insertion of the trocar to a convenient depth. It is very important, in order to avoid damage to intestines or even to retroperitoneal structures, to perform paracentesis at a location (usually pararectally to the left, somewhat underneath the navel) that has shown no resistance or tenderness at palpation. After careful local anesthesia, the patient is asked to distend the abdomen by forced pressure during the insertion of the trocar. A piece of polyethylene tubing is then introduced through the trocar about 15 cm. deeper into the abdominal cavity and the trocar is gently withdrawn. A flask of physiologic saline solution is connected to the tubing in the same way as for intravenous perfusion. If the saline solution flows continuously by gravity into the abdomen under only small pressure, one can be certain that the polyethylene tube is properly placed within the free abdominal cavity. After administration of about 200 ml. of saline solution, the injection of the colloidal gold, diluted with saline solution, is made and saline solution is again given for final dilution and dispersion of the radiocolloid within the abdominal cavity. In a few cases we have also added some anesthetic, the same as was used for the local anesthesia of the abdominal wall.

As soon as the intraperitoneal injection is completed, the polyethylene tube is removed and the puncture site covered with a small adhesive band. The patient is in-

structed to immediately start turning slowly in bed for a few hours in order to enhance even distribution of the administered colloidal gold within the abdominal cavity. The fluid is being dispersed by the combined effects of capillarity and hydrostatic pressure.

The author, as well as other workers, has consistently found that intraperitoneal and intrapleural administration of colloidal Au^{198} is a safe procedure, being by no means hazardous to the patient or the operator if carefully performed. Cases with marked loculations of the abdominal cavity due to adhesions, however, are not suitable for this therapy.

The majority of our patients were treated first by surgery and then by supplementary intraperitoneal colloidal radiogold, combined with the standard postoperative radiation therapy as practiced for many years. The latter consists of fractionated 250–400 kv. roentgen therapy with a total depth dose of at least 4,000 r within the pelvic cavity and the lower abdomen, and of 1,000–2,000 r within the upper part of the abdomen in most of the Stage III and IV cases. No such penetrating radiation, however, is administered to the immediately subphrenic structures. In addition, most of these patients received vaginal radium application (about 1,800 mg. hr.). Since the great majority had either supravaginal or total hysterectomy, only few intrauterine radium treatments were done with correspondingly higher dosage.

MATERIAL

The cases of the present series are defined with respect to histologic classification and anatomic extension stages of the ovarian neoplasms. This series concerns the common ovarian cancers only, the classification of which has been recently standardized at a special Conference by the Cancer Committee of the International Federation of Gynecology and Obstetrics (IFGO), so that in the future the therapeutic reports throughout the world may be accurately compared.* This new histologic classification is shown in Table I.

TABLE I

INTERNATIONAL CLASSIFICATION OF THE COMMON EPITHELIAL TUMORS OF THE OVARY (PROPOSED BY THE CANCER COMMITTEE OF THE IFGO)

1. *Serous cystomas*
   - (a) Serous papillary cystadenoma, benign
   - (b) Proliferating serous papillary cystadenoma without stromal invasion, possibly malignant
   - (c) Serous cystadenocarcinoma, all grades
2. *Mucinous cystomas*
   - (a) Mucinous cystadenoma, benign
   - (b) Proliferating mucinous cystadenoma without stromal invasion, possibly malignant
   - (c) Mucinous cystadenocarcinoma, all grades
3. *Endometrioid tumors*
   - (a) . . . (there is no agreement as to whether some cases of ovarian endometriosis may properly be classed as tumors)
   - (b) Proliferating endometrioid adenoma and cystadenoma, possibly malignant
   - (c) Endometrioid adenocarcinoma, all grades
4. *Undifferentiated carcinoma* (cell type unknown)

This classification is somewhat different from the one the author had established previously and used for many years (Table II); however, there exists a correlation between these two classification systems, as shown in Table III.

Owing to the fact that the proposed international classification is not yet in official use and since the number of cases in each of its groups would still be very small in our series, we have considered it advisable to retain our own previous somewhat simplified classification for this presentation. We have, however, started to classify the new cases, from the beginning of 1962 on, in accordance with this international proposal.

For the definition of the anatomic extension stages, we have kept our previous classification (Table IV) which we found adequate for a correct evaluation of the therapeutic results obtained from both

* This conference convened at the Radiumhemmet in Stockholm from August 24–26, 1961. Its members were the following: Drs. Lauren V. Ackerman, U. S.; George Gricouroff, France; H. Hamperl, Germany; A. T. Hertig, U. S.; H. L. Kottmeier, Sweden; J. H. Muller, Switzerland; L. Santesson, Sweden; Claud W. Taylor, England; Howard C. Taylor, Jr., U. S.; and G. Teilum, Denmark.

surgery and radiation therapy, with special consideration of routine intraperitoneal Au^{198} administration.

Staging of ovarian cancer has not yet been done along internationally accepted lines, but we believe that our tentative classification could be considered a suggestion in this direction. It is shown in Table IV. The accuracy of this staging has been somewhat enhanced at the Zürich Frauenklinik for several years by means of systematic biopsies taken from the omentum and the parietal peritoneum during operation of all ovarian neoplasms, as advocated by Professor Held.

RADIOACTIVE COLLOIDAL GOLD APPLICATIONS

As a rule, except in some cases of Stage IV with ascitic abdominal carcinomatosis, we start by giving fractionated roentgen therapy over a period of from 1 to 3 weeks. This has the advantage that rare postoperative complications will appear before the gold is administered and also allows the organism to become somewhat adapted to radiation; general reactions from radiogold applications are then, as a rule, only minimal. In order to avoid undue stress upon the patient, we never administer single doses of more than 150 mc in larger patients and 100–120 mc in smaller women. A second application may follow at an interval of from 4 to 5 weeks. Exceptionally, and in Stage III and IV cases only, a third and even a fourth treatment with radiogold will be administered. No rigid rules can, however, be established as far as these radiogold administrations are concerned since recovery rate and other complex factors, which play an important part in clinical radiation therapy, must be evaluated in each instance.

In general, one application is made in the cases in Stage I, one to two applications in Stage II cases and two to three applications in those of Stage III. For the cases in Stage IV, inasmuch as they appear to be incurable, both the dosage and the number of radiogold administrations are apt to vary greatly, since the purpose is to obtain prolongation of the life span with as little discomfort as possible.

Table II

THE AUTHOR'S HISTOLOGIC CLASSIFICATION OF THE COMMON EPITHELIAL OVARIAN TUMORS

Grade A:	Highly differentiated proliferating adenomatous and papillomatous growths of disputable histologic malignancy; however, clinically aggressive and even metastasizing within the abdominal cavity
Grade B:	Moderately differentiated adenocarcinomas and papillary carcinomas
Grade C:	Poorly differentiated solid carcinomas

Note: The compound borderline cases of Grade B and C were classified in accordance with the predominating type of cancer.

Table III

CORRELATION OF THE AUTHOR'S PREVIOUS HISTOLOGIC GRADING WITH THE CLASSIFICATION PROPOSED BY THE IFGO STUDY GROUP, STOCKHOLM, 1961

Grade A =	Groups 1b, 2b, 3b
Grade B =	Groups 1c, 2c, 3c
Grade C =	Group 4 and poorly differentiated cases of the preceding groups

RESULTS

The 5 year results obtained in this series of 118 unselected cases of common ovarian carcinoma, all treated in the described manner from the end of 1949 to the end of 1956 are summarized in Table V.

This table is presented in two sections. In the upper section, all cases are classified according to the histologic grades and the stages of extension. In the lower section the

Table IV

AUTHOR'S STAGING OF OVARIAN CANCER

Stage I.	Unilateral ovarian tumors without adhesions and without visible metastases
Stage II.	Adherent ovarian tumors Bilateral ovarian tumors Cystic tumors ruptured *before* operation Tumors with metastases limited to the pelvis
Stage III.	Cases as in Stage I and II, but with additional metastases within the great abdominal cavity if the latter deposits do not exceed 2.5 cm. (1 inch) in diameter
Stage IV.	All other cases of ovarian cancer

sum of cases in each stage and also the same sum, but with omission of the 12 histologic Grade A cases of questionable true malignancy, are listed.

DISCUSSION

From the results shown in Table v, it appears that routine intraperitoneal administration of colloidal Au^{198} can be considered as a progress in the treatment of ovarian cancer—a progress that is, however, limited mainly to the cases in Stage I and II. The over-all results, as indicated in the bottom row of the table, show that 43 per cent of the total number of unselected cases are alive after 5 years; and 38 per cent of the Grade B and C cases of indisputable carcinoma remain alive without evidence of cancer after 5 years. These figures compare favorably with statistics that concern only the cases on which radical operations were performed. For instance, the figures published from the First University Frauenklinik of Vienna show only a 47 per cent survival in a series of 68 cases operated on which were not treated with additional intraperitoneal radiogold.

It is further noteworthy that no case in Stage I died from cancer, and that only 28 per cent of the true carcinoma Stage II cases, of which many did not have radical operations, died from cancer. This means an over-all cancer mortality of the Stage I and II cases of only 14 per cent and of 16 per cent for the histologically unquestionable carcinomas.

For comparison, in an earlier series of 23 cases of true Stage I carcinomas which had been treated in our Hospital Unit with the same conventional surgical and radiothera-

TABLE V

COMMON OVARIAN CANCER—AU^{198} SERIES

	No. of Cases			Alive without Symptoms after 5 Years			Deceased from Carcinoma before 5 Years			Deceased from Intercurrent Disease		
Stage \ Grade	A	B	C	A	B	C	A	B	C	A	B	C
I	6	17	1	6	15	1	0	0	0	0	2	0
II	3	19	6	3	15	1	0	3	4	0	3	1
III	2	25	11	2	8	0	0	17	11	0	0	0
IV	1	18	9	0	0	0	1	18	9	0	0	0
I–IV	12	79	27	11 92%	38 48%	2 7·5%	1 8%	38 48%	24 89%	0 0	3 4%	1 3·5%
Stage \ Grades	A+B+C		B+C	A+B+C		B+C	A+B+C		B+C	A+B+C		B+C
I	24		18	22		16	0		0	2		2
II	28		25	19		16	7		7	2		2
I+II	52		43	41		32	7		7	4		4
III	38		36	10		8	28		28	0		0
IV	28		27	0		0	28		27	0		0
I–IV	118		106	51 43%		40 38%	63 53·5%		62 58%	4 3·5%		4 4%

peutic techniques, but without intraperitoneal radiogold, only 14 cases, *i.e.*, 60 per cent were salvaged. On the other hand, in spite of substantial palliative results, no case in Stage IV was saved despite the fact that occasionally fractionated doses of larger amounts of colloidal Au^{198}, up to a maximum of 800 mc, were used. Massive abdominal and evidently also extra-abdominal extension of ovarian carcinoma is and remains fatal.

Somewhat more encouraging are the results that were obtained with additional intraperitoneal gold therapy in the Stage III cases, where 8 out of 36, or 22 per cent, remained free of disease after 5 years. This is an appreciable progress since before the routine isotope administration such cases were but exceptionally controlled.

The prognostic significance of the histologic grade of differentiation of the ovarian epithelial neoplasms appears at first glance striking (lower row of the upper section of Table V) in that only 7.5 per cent of the predominantly solid, poorly differentiated Grade C cases have survived, whereas 48 per cent of the Grade B cases of moderately differentiated adenocarcinoma and papillary carcinoma were alive. The high figure of 92 per cent in the Grade A group is, of course, not surprising since these neoplasms are histologically of questionable malignancy; 1 case, however, was lost from intractable abdominal generalization.

This great difference in the results of the cases of histologic Grades B and C is also partly due to the fact that the majority of the Grade C cases are found in the advanced clinical Stages III and IV; this is in accordance with the particularly rapid growth rate of such poorly differentiated carcinomas. Their higher degree of malignancy is also supported by the observation that in the Stage II group, 4 out of 6 Grade C cases, but only 3 out of 19 Grade B cases died from cancer.

The routine intraperitoneal Au^{198} administrations were performed without any mortality related to the treatment. Thus, if correctly applied, intracavitary administration of colloidal Au^{198} is a safe procedure. All cases of this series which suffered from terminal ileus had, in fact, recurrent cancer.

Obviously, ovarian cancer remains primarily a "surgical" problem. However, the routine intraperitoneal administration of colloidal radioactive gold, even if often only on an apparently "prophylactic" basis, is an important adjuvant procedure due to the high incidence of early macroscopically invisible implants throughout the abdominal cavity which may already have occurred in about 50 per cent of the operable cases. This is confirmed by the study of Elkins and Keetel who made cytologic examinations of peritoneal washings, which were centrifuged and the sediment stained with Papanicolaou's stain. In 50 per cent of the operable cases of ovarian cancer with no rupture of the capsule and without evidence of dissemination outside of the ovary, these authors found active tumor cells. It is interesting that this percentage parallels almost exactly the number of these authors' cases which did not survive 5 years despite radical surgery. In contradistinction, no cases of the corresponding group of our own series additionally treated with colloidal radiogold have died from cancer, further indicating that the results obtained by means of routine administration of the colloidal Au^{198} are significant.

Similar good survival figures in the earlier stages of carcinoma of the ovary, treated with the addition of intraperitoneal radioactive colloidal gold, were reported at the 1961 Annual Meeting of the American Radium Society by H. B. Latourette and his University of Iowa Group.

Although ovarian (and tubal) cancer in its different stages of extension appears to be the main indication for intraperitoneal and intrapleural colloidal radiogold therapy, there are other indications for it, such as metastatic abdominal and pleural carcinomatosis from breast cancer, abdominal extensions of lymphosarcomas and reticulosarcomas, seminomas, etc., which in the author's experience respond well to this treatment. However, only palliative

results can be expected in most such conditions.

Encouraged by the good results of intraperitoneal radiogold therapy in still operable ovarian cancer, we have considered it also for the postoperative management of some other types of abdominal neoplasms, such as operated carcinoma of the cervix with histologic evidence of parametrial and lymph node metastases, and endometrial carcinoma of the uterus with ovarian metastases or metastases in the lymph nodes. The preliminary results are favorable. We have also administered intraperitoneal gold (with encouraging results) in a limited number of cases which were operated on for carcinoma of the colon and of the stomach and which showed evidence of beginning invasion of the lymphatic system. Of course, intraperitoneal radiogold therapy is not capable of preventing portal tumor dissemination (which accounts for at least 50 per cent of the metastases of such carcinomas), but owing to its particular mode of action, it is suitable for combatting efficiently early serosal and lymphogenic metastases.

Indeed, in the present state of development of intracavitary radiocolloid therapy, it is of importance that clinical workers in this field should gain further experience not only with colloidal Au^{198}, but also with other radiocolloids, such as radioactive colloidal chromic phosphate, radioyttrium, etc. We have used and intend to continue the use of colloidal radiogold therapy in order to maintain and enhance the scientific value of our series of treated patients.

SUMMARY

A report is presented of the 5 year results of routine intraperitoneal administration of colloidal radioactive gold (Au^{198}) for the treatment of ovarian cancer in an unselected group of 118 patients. These results indicate that such isotope administration may be evidence of progress in the field of cancer therapy, since it may increase the salvage rate of the ovarian cancer patients with surgically resectable primary lesions.

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CARCINOMA OF THE PALATINE ARCH*

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THE palatine arch includes the uvula, the soft palate, the tonsil and its bed, and the tonsillar pillars. Neoplasms arising from these structures are moderately common, being the second most common neoplasm of the upper air passages, the tonsillar region alone accounting for 1.5 to 3 per cent of all forms of cancer.[1]

The primary form of treatment of this cancer, because of its behavior, location and extent when first seen, is with rare exception not surgical; radiation therapy, usually beam therapy, is the treatment of choice. Radium implantations are, in general, technically difficult to do satisfactorily in this region.

MATERIAL

The material of the present study consists of 305 cases. It represents all known cancers of the palatine arch treated by beam irradiation as the primary treatment method at the Massachusetts General Hospital and the Massachusetts Eye and Ear Infirmary in the 20 year period prior to April, 1959.

AGE DISTRIBUTION PATTERN

This entity is primarily a disease of elderly males. Two hundred and fifty-eight or 85 per cent of the patients in this sample were males and only 47 or 15 per cent were females, with the highest numerical incidence in the seventh decade, though in the female this seems to occur somewhat earlier (Table I).

HISTOLOGIC DISTRIBUTION PATTERN

By far, the most common histologic types of cancer occurring on the palatine arch are the squamous cell carcinomas of varying degrees of differentiation accounting for 259 or 85 per cent. The ratio between males and females is essentially that of the frequency distribution (Table II). Seven per cent or 22 cases were recorded as transitional cell carcinoma, lymphoepithelioma or related neoplasms in which, however, there seems to be a relative predilection for females, the ratio being 1 to 2 against 1 to 9. Malignant lymphomas of varying types are for some reason, in this material, less numerous than is generally reported.

TABLE I

DISTRIBUTION BY AGE AND SEX

	Males	Females	Total
<20	0	0	0
20–30	2	0	2
30–40	1	1	2
40–50	19–65%	10–35%	29
50–60	62–80%	14–20%	76
60–70	87–90%	13–10%	100
70–80	68–90%	5–10%	73
80+	19	4	23
Total	258–85%	47–15%	305

An attempt to relate the histologic pattern to the structure of origin was not very satisfactory because of uncertainty of site of origin of the disease in most instances. In those situations in which the disease could be relegated to one site with certainty all were found to be of the squamous cell carcinoma, except for the tonsillar region where of 33 so determined 6 were malignant lymphomas, 6 transitional cell carcinoma, lymphoepithelioma or undifferentiated carcinoma and 1 a myeloma, leaving 20 still classified as epithelioma (Table III).

ANATOMIC DISTRIBUTION PATTERN

In the literature diseases of the palatine arch are discussed under the various sites

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TABLE II

DISTRIBUTION BY HISTOPATHOLOGY

	Males	Females	Total
Squamous Cell Carcinoma	228—88%	31—12%	259—85%
Grade 1			16
Grade 2			103
Grade 3			73
Grade 4			7
Not Mentioned			60
Transitional Cell Carcinoma	6	3	9
	65%	35%	7%
Lymphoepithelioma	8	5	13
Undifferentiated Carcinoma	3	2	5
Malignant Lymphoma	10	6	16
Plasma Cell Myeloma	2		2
Adenocarcinoma	1		1
Total	258	47	305

of origin with varying prognoses and behavior patterns. In the present material, in only 50 instances could a single structure be identified as the site of origin (Table III). In the vast majority of situations multiple areas of involvement were the rule, and the likely site of the original primary was not recorded. By far, the most common structure involved was the tonsil and tonsillar area, almost all nonepitheliomatous cancers involving this structure and two-thirds of the epitheliomas (Table IV). The anterior pillar and soft palate were involved only slightly less often in squamous cell carcinoma, relatively less frequently in other cancers. Most certainly, the site of origin of some of these was the anterior pillar and soft palate even though they could not be so certified.

TABLE III

ANATOMIC DISTRIBUTION WHEN ONLY ONE STRUCTURE WAS INVOLVED

Uvula Alone	1
Soft Palate Alone	7
Anterior Pillar Alone	9
Tonsil and/or Fossa	33
Total	50

Note: All confined cases were squamous cell carcinomas except those in the tonsil, of which 20 were squamous cell carcinomas, 6 lymphomas, 3 transitional cell carcinomas, 2 lymphoepitheliomas, 1 myeloma and 1 undifferentiated carcinoma.

THE PATTERN OF SYMPTOMATOLOGY

In 253 patients, records of reliable symptoms were available. The most common complaint which brought the patient to the doctor was sore throat (Table V). Other primary complaints in decreasing order of frequency were a sensation of a lump in the throat, a lump in the neck, pain on swallowing, pain in the ear, and least frequent, bleeding. Nine or about 5 per cent were without symptoms and the cancer was found on routine physical examination.

TABLE IV

AREAS OF INVOLVEMENT BY PRIMARY LESION AND ITS EXTENSIONS: FREQUENCY OF INVOLVEMENT

Area	Squamous Cell Carcinoma	Other	Total
Uvula	28 (11%)	2	30
Soft Palate	129 (50%)	12 (30%)	141
Anterior Pillar	170 (65%)	19 (40%)	189
Tonsil and/or Fossa	174 (65%)	45 (98%)	219
Tonsillar Lingual Fold	108 (40%)	13 (30%)	111
Posterior Pillar and Pharyngeal Wall	54 (20%)	19 (40%)	73
Tongue	83 (30%)	9	92
Retromolar Trigone	40 (15%)	0	40
2 Concomitant Areas	21 (8%)	3	24
Total	259	46	305

TABLE V

PRESENTING COMPLAINT

Sore Throat	120
Pain on Swallowing	21
Pain in Ear	11
Lump or Ulcer in Throat	41
Lump in Neck	38
Bleeding	6
Other	7
Symptomless	9
Total	253

The primary symptom was endured by the patient for less than 3 months by about one-half, less than 6 months by about one-fifth, and for more than a year by a surprising one-tenth of the patients recorded (Table VI).

RESULTS OF TREATMENT

In attempting to assess the results of treatment certain baselines were established: (1) It is recognized that cancers of various sites of origin and histology have different behavior patterns. This is well documented in the literature. Because of the uncertainty of this information in the present material, except in an insignificant sample, in most instances a detailed assessment on an anatomic basis was not feasible and except where specifically noted no anatomic distinction could be made. (2) The nonsignificant size of the sample of nonepitheliomatous cancers required that in many instances the study be confined to squamous cell carcinomas only. (3) Except where otherwise noted, lost patients are counted as failed or dead of disease at the time period next following the last entry.

TABLE VI

DURATION OF SYMPTOMS

<3 mo.	136
3–6 mo.	56
6 mo.–1 yr.	32
>1 yr.	20
Phys. exam.	9
Total	253

(4) Except where otherwise noted, a 3 year period was taken as the basis for follow-up since in this material in 78 per cent of the patients the failure to control the primary disease by the primary treatment occurred within 1 year, in 85 per cent within 3 years, and in only 12 per cent after 5 years. In the case of regional metastases present at the time of the primary treatment, failure to control such metastases was evident within 1 year in 85 per cent and within 3 years in 90 per cent. Less than 10 per cent of the failures of control of lymph node metastases occurred after 5 years. Because of the advanced age of the patients with this disease, simple survival as a criterion of treatment effectiveness may be misleading.

It is generally accepted that the size of the primary lesion and the presence and extent of the metastases at the time of the initial treatment—other things being equal—have great influence on survival. With this in mind the effect of the primary radiation therapy on the control of the disease as represented by survival without disease was examined by classifying tumors according to the T.N.M. system and histology (Table VII).

The survival pattern of 259 squamous cell carcinomas is shown in Table VIII. Only a gross number of 56 patients, or 22 per cent, remained free of disease 3 years or more; however, 50 per cent of T_1 N_0 cases survived 3 years, 30 per cent of the N_0 patients and 20 per cent of N_1 cases. If those

TABLE VII

T.N.M. CLASSIFICATION (I.U.A.C.)

T_1—Primary less than 3 cm. in size
T_2—Primary 3–5 cm.
T_3—Primary greater than 5 cm. with limited extension
T_4—Massive
N_0—Regional lymph node metastases not mentioned or none present
N_1—Lymph node single <3 cm. or 2 adjacent <2 cm. each
N_2—Single >3 cm.—movable or multiple unilateral
N_3—Single >3 cm.—fixed or bilateral
M—Distant metastases

TABLE VIII

SQUAMOUS CELL CARCINOMA OF PALATINE ARCH
SURVIVAL WITHOUT DISEASE—3 YR.

T \ N	0	1	2	3	M
56 (1)	39/20	4/2	6/2	6/1	1/0
109 (2)	54/16	18/5	16/2	20/0	1/0
74 (3)	32/4	13/1	15/1	14/0	
20 (4)	5/1	3/0	1/0	10/1	1/0
259/56	130/41	38/8	38/5	50/2	3/0

with massive local tumor, T_4, are eliminated, there was no significant improvement. No patients with remote disease survived 3 years.

The survival pattern of 22 patients with lymphoepitheliomas, transitional cell carcinomas and other related neoplasms is shown in Table IX. The numbers are too small to be of statistical value but do indicate curability of the disease in accordance with published figures.

The pattern of behavior of malignant lymphomas is shown in Table X.

Of 5 patients with undifferentiated carcinomas, 2 (T_3 N_3 and T_3 N_0) survived less than 1 year; 1 (T_2 N_3) survived less than 2 years; 1 (T_4 M) survived less than 6 months and only 1 (T_3 N_0) is living free of disease now at 8 years.

These figures represent our experience and are not presented as results attainable. Compared to the results reported by others, these are not impressive.

TABLE IX

LYMPHOEPITHELIOMA AND TRANSITIONAL CELL CARCINOMA; SURVIVAL WITHOUT DISEASE—3 YR.

T \ N	0	1	2	3	M
4 (1)	3/1	1/0	0/0	0/0	0/0
12 (2)	3/1	3/2	2/0	2/0	2/0
4 (3)	1/0	0/0	0/0	3/0	0/0
2 (4)	0/0	0/0	1/0	0/0	1/0
22/4	7/2	4/2	3/0	5/0	3/0

THE EFFECT OF INVOLVEMENT OF VARIOUS STRUCTURES ON SURVIVAL OF PATIENTS WITH SQUAMOUS CELL CARCINOMA

Certain combinations of disease have in the folklore of cancer management come to be taken as indicative of grave prognosis; for example, involvement of the lingual tonsillar fold or extensions into the base of the tongue or lateral pharyngeal wall. With this in mind these various combinations of extensions were examined with regard to their effect on the pattern of survival, free of disease (Table XI). The most serious combination of sites of involvement seems to be that of two or more concomitant but separate sites of involvement where survival was reduced to less than 1 per cent. Involvement of the lateral pharyngeal wall, the posterior pillar and of the musculature of the tongue apparently reduces the salvage rate appreciably, but involvement of the lingual tonsillar fold which is traditionally taken to augur a bad prognosis—the so-called graveyard triangle—did not live up to its bad reputation. Eighteen of 108 instances of such involvement or about 15 per cent survived free of disease 3 years or more.

THE EFFECT OF VARIOUS OTHER FACTORS ON TUMOR CONTROL AND SURVIVAL

Aside from the size of the tumor, its histologic nature and state of advancement, one of the most potent factors affecting tumor control in patients treated by radiation therapy should be the size of the tumor dose. With this in mind, control for the duration of the patient's life or of follow-up

TABLE X

MALIGNANT LYMPHOMA
SURVIVAL WITHOUT DISEASE—3 YR.

T \ N	0	1	2	3	M
5 (1)	3/2		1/0	1/0	
7 (2)	5/2			1/1	1/0
3 (3)	1/0	1/1		1/0	
1 (4)				1/0	
16/6	9/4	1/1	1/0	4/1	1/0

TABLE XI

EFFECT OF INVOLVEMENT OF VARIOUS STRUCTURES ON SURVIVAL OF PATIENTS WITH SQUAMOUS CELL CARCINOMA OF PALATINE ARCH

	No. of Patients	3 Yr. Control		Involvement Limited to Structure	
				No. of Patients	3 Yr. Control
Total No.	259	56	22%		
Uvula	28	5	18%	1	1
Soft Palate	129	18	14%	7	2
Anterior Pillar	170	35	21%	9	4
Tonsil and/or Fossa	174	33	19%	33	7
Tonsillar Lingual Fold	108	18	16%		
Posterior Pillar and Pharyngeal Wall	54	6	11%		
Tongue	83	11	13%		
Retromolar Trigone Alveolar Ridge-Buccal Mucosa	40	10	25%		
2 Concomitant and Unrelated Areas	21	1	0.5%		

Note: All confined cases were squamous cell carcinomas except those in tonsil, of which 20 were squamous cell carcinomas, 6 were lymphomas, 1 myeloma, and 6 other.

of both the primary lesion and the lymph node metastases present at the time of first treatment was evaluated as a function of estimated tumor dose (Table XII). (The additional effect of time is recognized and taken into account.)

Control of the primary lesion occurred in less than one-half when the tumor dose was less than 3,000 r in 2 to 3 weeks, and control of the lymph node metastases did not occur. With increasing dose, increasing expectancy of tumor control is evident. In the 5,000 to 7,000 r range, about three-fourths of the primary lesions and one-half of the lymph node metastases were controlled; and when the dose reached 7,000 r or more, given at the rate of 1,000 to 1,250 r per week, only about one-tenth of the primary lesions failed to be controlled and control of the lymph node metastases increased proportionately. Local control does not mean cure, but doses of this order do permit the

TABLE XII

CONTROL OF THE PRIMARY LESION AND LYMPH NODE METASTASES AS A FUNCTION OF TUMOR DOSE AT INITIAL TREATMENT

Tumor Dose	No. of Patients	Primary Lesion		Lymph Node Metastases		Lost
		Controlled	Not Controlled	Controlled	Not Controlled	
<3,000 r	23	9–40%	13–60%	0	12	1
3–5,000 r	73	45–65%	26–35%	10	26	2
5–7,000 r	181	131–75%	44–25%	40	42	6
>7,000 r	28	27–95%	1– 5%	6	1	
Total	305					

TABLE XIII

CONTROL OF PRIMARY LESION AND LYMPH NODE METASTASES AS A FUNCTION OF RADIATION QUALITY

	Supervoltage				
	Primary Lesion		Lymph Node Metastases		
	Controlled	Not Controlled	Controlled	Not Controlled	Lost
P.+L. N.	39		39		6
P.+L. N.		26		26	
P. only	95				
P. only		14			
P.+L. N.	9			9	3
Total	143	40	39	35	
	Orthovoltage				
P.+L. N.	17		17		
P.+L. N.		28		28	
P. only	34				
P. only		16			
P.+L. N.	18			18	
Total	69	44	17	46	

patient, if not cured, to die of some other, perhaps less distressing, manifestation of his disease rather than of locally persistent and growing cancer.

This indication of increasing tumor control as a function of increasing tumor dose is supported by an evaluation of the effectiveness of supervoltage therapy as compared to orthovoltage therapy (Table XIII). In this evaluation it is seen that control of the primary lesion, when treated by supervoltage occurred more than three times as often as failures, compared to less than twice as often as failures when orthovoltage was used. Failure of control of the cervical lymph node metastases equalled control, whereas failure occurred three times as often as control when lower voltages were employed. Aside from the obvious value of experience, this may be taken as a reflection of the increased efficiency of supervoltage as a means of securing adequate tumor doses and also of the improved techniques which the use of supervoltage engenders.

EFFECT OF SEX ON TUMOR CONTROL

In a recent publication,[4] sex was indicated as the principal correlative of survival in patients with cancer of the tonsil. In the present material (Table XIV) the ratio of control to non-control of metastases was not significantly different in the two sexes; about 1 to 1.5 control of the pri-

TABLE XIV

CONTROL OF PRIMARY LESION AND LYMPH NODE METASTASES AS A FUNCTION OF SEX

	Females				
	Primary Lesion		Lymph Node Metastases		
	Controlled	Not Controlled	Controlled	Not Controlled	Lost
P.+L. N.	10		10		
P.+L. N.		14		14	
P. only	19				
P. only		3			
P.+L. N.	1			1	
Total	30	17	10	15	
	Males				
P.+L. N.	46		46		9
P.+L. N.		40		40	
P. only	110				
P. only		27			
P.+L. N.	26			26	
Total	182	67	46	66	

Table XV

METASTASIS DEVELOPING DURING THE COURSE OF DISEASE

Lung and Mediastinum	19
Liver	1
Bone	10
Peripheral	16
Widespread	6
Skin	3
Nerve	2
Abdomen	2

mary lesion, however, seems to favor males, the ratio of controls to failures being 3 to 1 in males and 2 to 1 in females. The conclusion may be drawn from this material at least that sex is not all that important.

THE PATTERN OF METASTASES, COMPLICATIONS AND DEATH

During the course of the disease remote metastases do occur, though in this material not as often as expected, due perhaps to limited survival. The pattern is shown in Table xv. Lung and mediastinal metastases, peripheral lymph node metastases and bone metastases were most common, occurring in 19, 16 and 10 instances, respectively. The low recorded incidence of liver metastases may be an indication of data inadequacy.

Complications as the result of vigorous radiation therapy are to a degree unavoidable but should by modern techniques be minimal. In the present material serious complications occurred in 76 patients or in about one-fourth of the patients treated, approximately equal to the over-all rate of cure. The most common complication, which is more annoying than serious, was dry mouth, being recorded as significant in 38 cases and being the only complication in 31 patients. Other complications are more serious and often lethal, the most common being soft tissue necrosis, usually over the inner aspect of the mandible, which occurred 17 times as the sole complication and was present in about 31 or about 10 per cent of all patients. Hemorrhage was the principal complication in 19 patients and occurred in 23 patients. Bone necrosis occurred in 17 patients. No patients developed radiation myelitis (Table xvi).

The terminal status of the patients, the mode and cause of death when determinable is shown in Table xvii in both patients with and without demonstrated local activity of the disease at the time. Intercurrent disease and a second cancer were the most frequent known causes of death in those patients in whom the primary disease remained controlled, occurring in 14 and 19 instances respectively out of a total of 95. When the primary disease was not controlled—the state of affairs in 210 cases—massive extension of the primary lesion was the most common cause of death, accounting for more than 10 per cent of the failures, followed by generalized metastases, starvation, and hemorrhage, which occurred only slightly less frequently. Intercurrent disease as the cause of death as would be expected was overridden by other causes.

MULTIPLE PRIMARY LESIONS

The occurrence of multiple primary carcinomas in the air and food passages in susceptible patients is well known. In this material, 59 patients or 19 per cent had another primary carcinoma sometime during their lifetime and 16 patients developed a third or fourth cancer. Most of these were squamous cell carcinomas and all but 12 were in the upper food or respiratory tract (Table xviii). The palatine arch, oral cavity and larynx were the most common sites of

Table XVI

COMPLICATIONS

	Primary	Secondary
1. Dry Mouth	31	7
2. Necrosis of Soft Tissue	17	14
3. Osteomyelitis and Osteonecrosis	8	9
4. Pain Requiring Surgery	6	3
5. Hemorrhage	19	4
6. Radiation Myelitis	0	0
7. Skin Necrosis	4	1
8. Dental Complications	6	0
9. Other	16	0

TABLE XVII

STATUS, CAUSE AND MODE OF DEATH WHEN DETERMINABLE

	Without Known Disease	With Disease
Total No.	95	210
With Primary Lesion	0*	129*
With Primary Lesion and Secondary Metastases	0*	18*
Second Cancer	14*	7*
Intercurrent Disease	19*	6*
Unknown	28*	45*
Massive Extension of Primary Lesion	0	26
Surgical Complication	0	1
Generalized Metastases	0	18
Cerebral Metastases	0	1
Hemorrhage	0	13
Inanition	0	19

* Plus those living = total number.

TABLE XVIII

SECOND PRIMARY CANCER ASSOCIATED WITH CANCER OF THE PALATINE ARCH

Location of Second Primary Lesion	Squamous Cell Carcinoma	Total No.
Palatine Arch	13	14
Oral Cavity	11	12
Hypopharynx	5	5
Larynx	8	9
Esophagus	4	4
Lung	3	3
Outside Upper Food and Air Passages	9	12
Total	53	59

Sixteen patients developed a third or fourth primary cancer.

occurrence. Ten of the associated neoplasms occurred prior to the onset of the palatine disease and 17 occurred 3 or more years after treatment of the original primary lesion which represents an incidence of about 25 per cent of the 76 patients at risk.

SUMMARY AND CONCLUSIONS

Three hundred and five cancers arising on the various structures of the palate and arch treated by beam irradiation at the Massachusetts General Hospital were reviewed with regard to age and sex distributions, histologic pattern, results of treatment and association of multiple neoplasms.

This is primarily a disease of males of advanced years with a squamous cell carcinoma the most common histologic type. Failure to control either the local or regional metastases was evident in more than 80 per cent of the patients within 3 years and for this reason a 3 year follow-up period gives a reasonable indication of the effectiveness of treatment.

A gross 3 year cure rate of 22 per cent occurred in all squamous cell carcinoma cases; however, there was a cure rate of 50 per cent of T_1 N_0 cases, and early regional lymph node involvement still permitted a 20 per cent 3 year survival.

Frequency of control of local disease is a function of tumor dose; 7,000 r in 6 weeks resulted in only about 10 per cent local failure, whereas less than 3,000 r controlled no lymph node metastases and less than one-half of the primary lesions of all histologic types. Such doses are accomplished more effectively by supervoltage radiation.

Multiple primary cancers of the air and food passages occur in about 20 per cent of all patients and about one-fourth of those who survive the original disease by 3 years or more.

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NASOPHARYNGEAL RADIUM APPLICATOR

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INTRACAVITARY irradiation of the nasopharynx has been performed in many ways, most of which offer some difficulty in accurate dose determination. A radioactive source placed in a mold of the nasopharynx has the main advantage of accurate placement of the radioactive sources in relation to the tumor. Suit *et al.*[4] described the construction of such a mold using dental plastic materials. This technique required the patient to be under general anesthesia for 60 to 75 minutes. We have recently constructed a similar mold requiring 15 minutes under general anesthesia and using no special apparatus. Details of construction and use of the device in a case of recurrent lymphoepithelioma of the nasopharynx are described.

CONSTRUCTION OF THE MOLD

A material in current use for making dental impressions is a hydrocolloid plastic called Alginate (Coe Laboratories, Inc.). The material is supplied as a dry powder which forms a thick paste when mixed with the prescribed amount of water. The paste acquires a soft rubbery consistency at body temperature within a few minutes.

During the biopsy procedure with the patient under general anesthesia, a volume of Alginate was prepared and packed into the nasopharynx through the mouth until it protruded from the oropharynx. By taking a sample of the unused material between the fingers, it was determined when the material had become firm (3 to 4 minutes). The soft mold was then removed from the patient by grasping the part protruding from the oropharynx with a hemostat. It was immediately washed in cold water and wrapped in a damp sponge since the material becomes dehydrated and deformed quite readily if not kept moist. Using this soft mold as a template, the dental prosthetics department was able to construct a hard mold of clear acrylic plastic.

Holes were drilled into the acrylic mold to receive radium needle sources and to provide anchor points for strings which would facilitate placement and removal of the mold (Fig. 1). Dummy needles were placed in appropriate holes and the mold was positioned in the patient on the following day. Roentgenograms of the skull were obtained

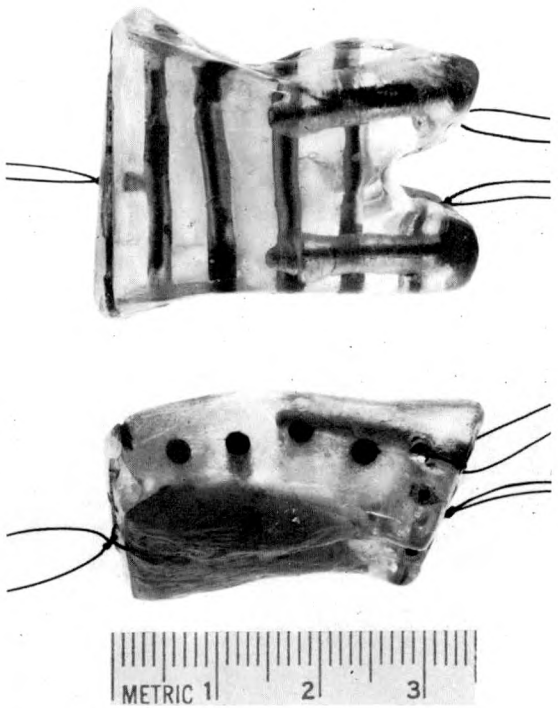


FIG. 1. Plastic nasopharyngeal radium applicator. Note holes for radium needles and the two anterior strings which anchor the device in place through the nasal passageways. The posterior string passes through the mouth and is taped to the cheek to facilitate removal.

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This material has been reviewed by the Office of the Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any endorsement of the opinions advanced or any recommendation of such products as may be named.

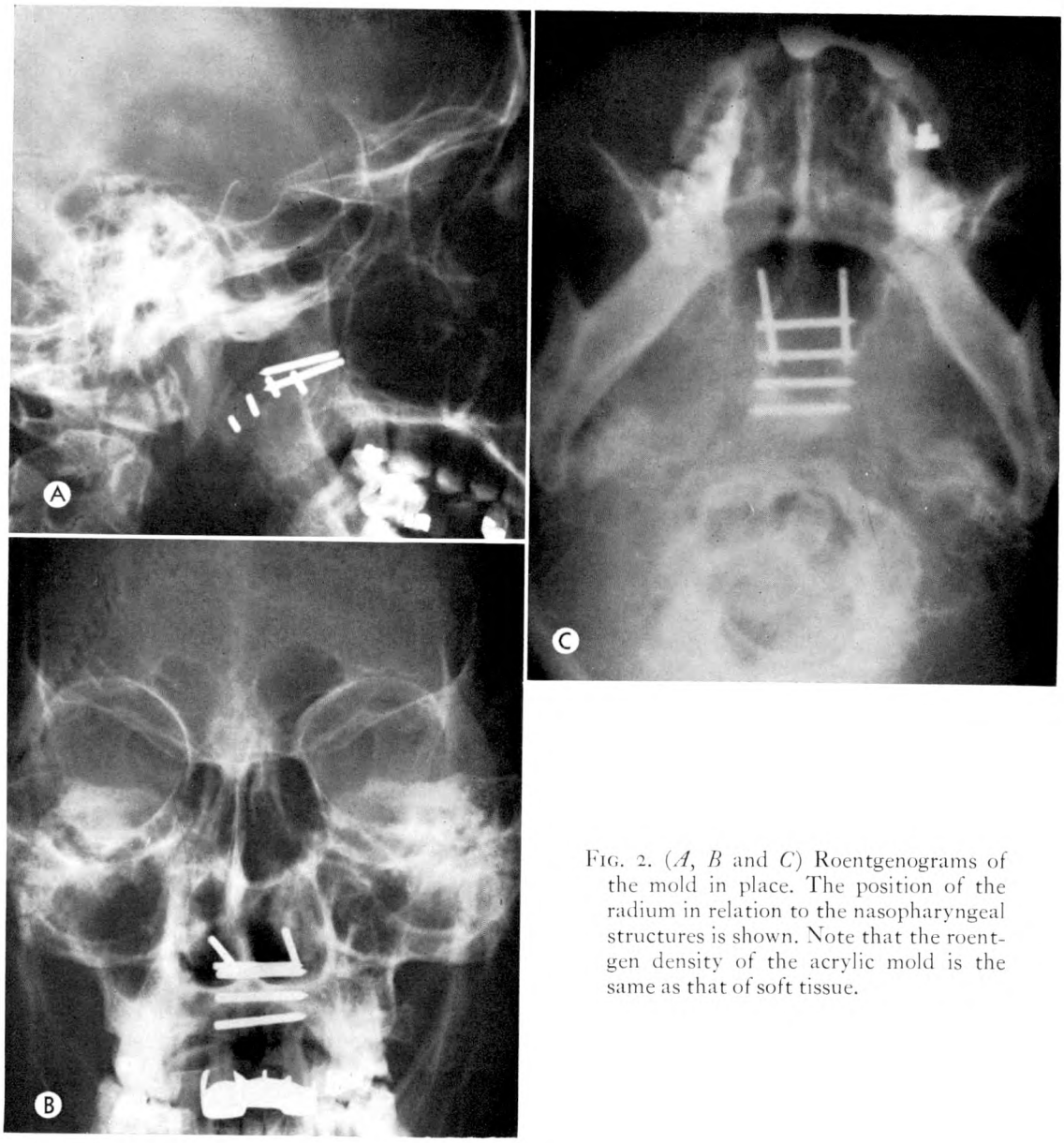


Fig. 2. (*A*, *B* and *C*) Roentgenograms of the mold in place. The position of the radium in relation to the nasopharyngeal structures is shown. Note that the roentgen density of the acrylic mold is the same as that of soft tissue.

and it was noted that there would be a low dosage area at the anterior margin of the nasopharyngeal roof since the anterior needle was limited in its forward position by the posterior margin of the nasal septum. It was apparent that there had been a slight change in the anatomy of the nasopharynx with the patient awake and upright. Holes were drilled longitudinally over the anterior half of the mold to accommodate two more needles. The anterior ends of these needles extended into the posterior nares. Addition of dental wax to the anteroinferior surface of the mold compensated for the change in position of the soft palate. When the mold was again positioned the posterosuperior surface was demonstrated to lie in contact with the tumor and roof of the nasopharynx. The applicator was again removed and the dummy needles replaced with radium sources which were sealed in place by soft dental wax.

THE CLINICAL PROBLEM

The patient had been treated at another hospital 2 years previously by 2 mev. rotational therapy to a total dose of 5,000 r to the nasopharynx. He presented with brisk epistaxis and gross recurrent tumor in the roof of the nasopharynx. No evidence of disease beyond the nasopharynx could be elicited, and it was decided to try to deliver a curative dose with radium. The patient was given eight treatments of $7\frac{1}{4}$ hours each over a 10 day interval. Daily roentgenograms of the skull obtained after insertion showed no measurable changes in the position of the mold from day to day (Fig. 2, *A*, *B* and *C*). Slight edema of the palate and nasopharynx was present during the last two treatments but offered no problem in placement of the mold. Because a curative dose was intended, points at the base of the tumor (bony roof of the nasopharynx) were chosen to receive the minimum tumor dose instead of calculating dose delivered to the surface of the mold as is the usual practice. The total dose delivered required calculation of the contribution of each source to each selected point. The distances from source to tumor were measured directly on the roentgenograms and were modified by the distortion factor obtained by comparing the distance between two sources on the roentgenogram with their known separation in the mold. Since the roentgen density of the mold is the same as that of soft tissue, no account was taken of attenuation in the mold.

Doses delivered varied from 4,760 r at the superior margin of the posterior choanae to 7,550 r at the posteroinferior margin of the nasopharynx. The dose to the palate and nasopharyngeal mucosa was necessarily large but somewhat protracted, and was apparently well tolerated. Examination of the nasopharynx 7 months after therapy revealed no evidence of recurrent tumor and slight crusting of the mucosa. The patient has experienced no discomfort whatsoever since the acute radiation reaction subsided.

SUMMARY

The construction by means of dental plastic materials and the use of a nasopharyngeal radium mold are described. The device has the important advantage of faithfully reproducible geometry of the radioactive sources with respect to the part irradiated despite repeated removal and reinsertion. The advantages of the use of similar molds in other tumor cases can be implied.

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AN AID IN THE PLANNING AND TEACHING OF RADIATION IMPLANTS*

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THE limited ability and experience of many radiologists in the use of radium can probably be traced to two factors: (1) minimal or no training with this therapeutic tool during the period of residency, and probably more basic, (2) a lack of interest in radium therapy in many of the radiologic training centers.

It is granted that the peculiar position in therapy formerly occupied by radium has changed somewhat in the past few years. There are now available more powerful roentgen ray machines, and more recently, large numbers and amounts of isotopes. All of these serve to give the radiologist a wide choice of methods when planning treatment. The selection of a treatment plan, however, should not be made because experience is limited to only one approach to a therapeutic problem, but, ideally, should be made after considering many factors, such as the particular lesion, the therapist's experience and knowledge concerning the pathologic and clinical behavior of the lesion, and finally a personal preference by the therapist for one plan or another.

Few therapists in general radiology vary their treatment methods significantly after a certain facility has been obtained in one method or another, however limited those methods may be. Satisfactory results may be obtained in many cases, but eventually it is almost certain that some tragic failures will occur because of inability, through inexperience, to select the best method of radiation. It is therefore a prime responsibility of the radiologic training center to make available to the resident a reasonably wide experience with all major therapeutic procedures—including radium—since some elementary ease in handling all therapeutic methods is a basic requirement for the radiologist. Certain lesions may be peculiarly suited to one or another mode of irradiation, but the well-trained therapist must be familiar with more than one acceptable method of treatment if for one cause or another the individually preferred method does not suit a particular therapeutic problem.

The reason claimed by many teaching departments for the minimal use of radium is the scarcity of suitable clinical material. This scarcity may be a real, a relative or an imagined condition. However, it should always be a challenge to extract all possible experience from each case. With some imagination and forethought each case can and should be studied and reviewed so that all members of the staff can participate in the planning. To increase the experience possible with a small patient load, the following idea was conceived as at least a partial solution. It has worked so well that a summary is given to demonstrate what we think is a simple but a valuable teaching aid. We believe it will offer assistance to the teaching program where scarcity of material demands that each case be utilized to the fullest. Even with plentiful material, it offers any radiologist a method of planning in some detail an implant that can be visualized easily in three dimensions, and it is subject to corrective change before the actual therapy is started.

METHOD

Ordinary plastic modeling compound, obtainable at most toy or hardware stores

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is used, and with no particular artistic skill but with some care, models of many anatomic parts can be fashioned. These models are made life size, and onto them are worked pathologic lesions, either similar to the one under discussion and planning or an assumed one for broadening experience. Radium molds can likewise be designed. Radium needles or radon seeds are simulated by wire or finishing nails of proper diameter and length. In our clinic 1 mg. of radium per cm. (active length) is standard, with 2 and 3 mg. needles in use. Wire lengths were therefore cut in 26 mm. and 34 mm. lengths. These dummy needles are handled with forceps and all protective measures are observed just as when radium itself is being used.

An actual case that came into the department presented an ulcerating lesion of the anterolateral margin of the tongue. A tongue model was fashioned, including a similar pathologic lesion, and then placed in a skull (Fig. 1). This was to further simulate working conditions in a lingual implant, suggesting the bony limitations in handling forceps and the radium needles. The teeth were separated for a distance of 3 cm., approximately the actual size of the mouth opening. After a preliminary discussion of the most effective method of handling the lesion, the implantation was carried out under supervision. Specifically, in this case, it was decided that a dose of 8,000 r_γ was desirable for a 2 cm. ulcerating lesion. Five

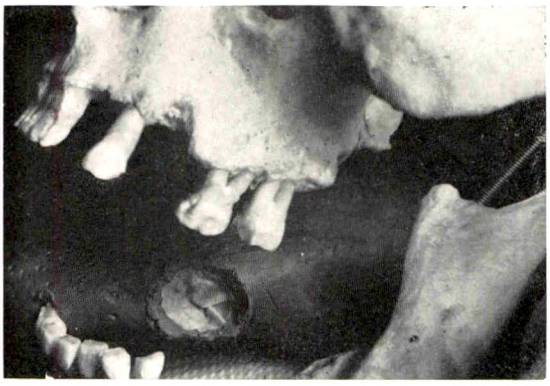


Fig. 1. Simulated carcinoma fashioned on border of tongue.

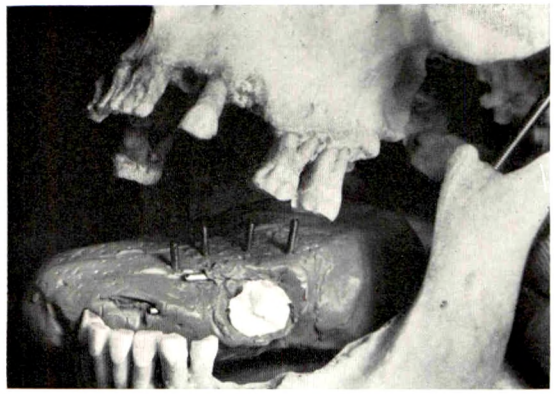


Fig. 2. "Carcinoma" implanted with the dummy radium needles. For clarity, they are left protruding more than if they were actual radium needles.

2 mg. and two 3 mg. needles were used in the implant as shown (Fig. 2). Subsequent roentgenograms of the implant (Fig. 3 and 4) were taken and the dosage was estimated just as for an actual implant. In this case, it was decided that additional external radiation would probably be added to a real lesion of this size and location.

The actual dosage in this example is not important, as the demonstration of the method has been our aim. Likewise, this experiment is not suggested as a substitute for actual clinical experience, but as an aid that can be used to supplement and expand that experience.

The disadvantages are obvious: the "feel" of inserting needles into live tissue is

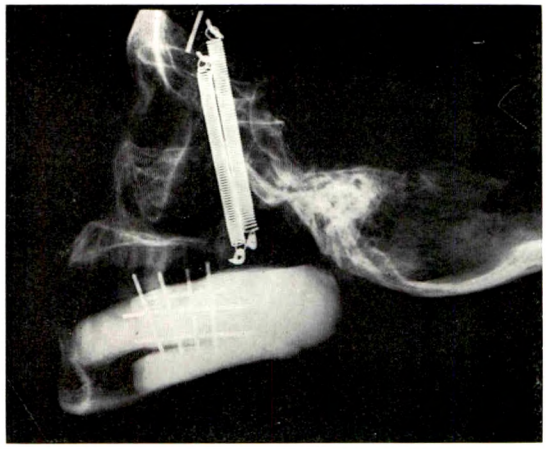


Fig. 3. Lateral roentgenogram to show the distribution of the radium needles in this projection.

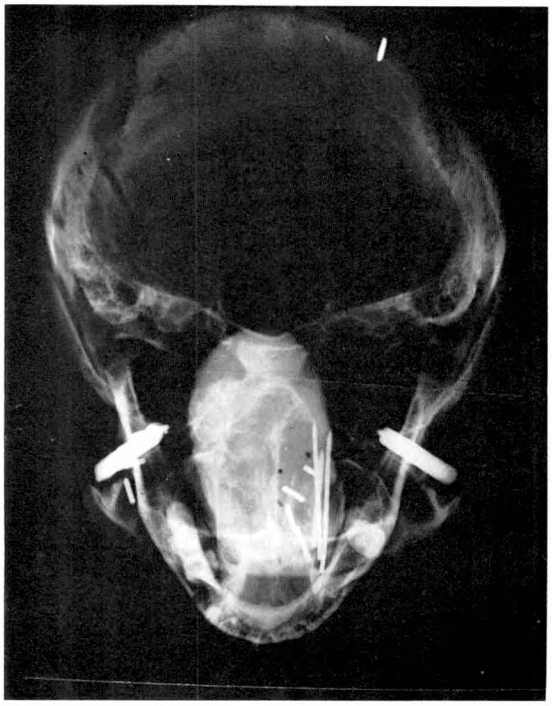


FIG. 4. Verticomental roentgenogram.

different from that of the plastic, and the complications (bleeding, patient response, problems of analgesia and anesthesia, etc.) are not evident. The greatest difference and experimental loss are that the clinical response to therapy is not obtained and the radiation effect, so important in judging the success of therapy, is not seen.

The plastic model is suggested to stimulate interest and to increase facility in the use of radium. Specifically, the therapist may receive a better idea of the volume of tissue involved for any individual lesion, and the limitations of space for inserting radioactive foci. It is believed such a method offers a means of estimating more closely the most effective arrangement for maximum dosage prior to implanting the actual lesion. We believe that the model is also useful as a method of demonstrating some of the hazards of radium by enabling the therapist to visualize adjacent anatomic structures such as the mandible which may require protection.

SUMMARY

Skill in the use of radium by radiologists has not been maintained in recent years not to the detriment of the radiologic profession necessarily, but more directly to the patients. This loss may be (1) the result of a lack of interest in the training program, or (2) paucity of clinical material. The former is inexcusable if the training center is to maintain expected standards. With basic interest in radium therapy, most related problems in a department can be overcome, or at least minimized. A simple procedure is described which is believed to offer merit in obtaining a maximum experience from a minimum amount of clinical material. It is also of value in planning implants at any time and anywhere, regardless of patient load and diversity of available clinical material. It should be of assistance to any radiologist who is interested in developing or teaching the use of interstitial radiation.

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A CASE OF A RECURRENT CHONDROSARCOMA OF THE MAXILLA TREATED UNSUCCESSFULLY WITH SULPHUR 35*

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IN AUGUST, 1958 Andrews and co-workers[1] reported the arrest of growth of a chondrosarcoma for a period of 5 months after the administration of 1 c of sulphur 35. Gottschalk[2] treated 3 patients in 1958 with amounts varying between 559 and 926 mc of S^{35} and noted a temporary cessation of growth of the chondrosarcomata for periods of 80 days to 3 months.

Their data indicated a relatively high uptake of the isotope in the chondrosarcomata as well as in normal cartilage. The bone marrow showed a high concentration for a very short time after the isotope administration, whereas the rate of disappearance from cartilage and chondrosarcoma was much slower. The S^{35} was found initially in the chondrocytes and later in the intercellular matrix in which the chondroitin sulfate is bound to protein. In the present report, we would like to relate our experience with a patient having a recurrent chondrosarcoma of the maxilla who was treated with 1,200 mc of S^{35}.

REPORT OF A CASE

The history of this 35 year old mother of 3 children begins in July, 1956 with a tooth extraction and curettage of a small radiolucent area in the right upper maxilla. A tumor of the right maxillary antrum was suspected. Four months later, in November, 1956, she had a resection of a tumor which involved the lateral wall of the right maxillary sinus and which was diagnosed as a chondrosarcoma. The sarcoma recurred 4 months later. In June, 1957 a partial right maxillectomy with removal of parts of the zygoma and the hard and soft palate was performed. The patient was seen for the first time at Montefiore Hospital in December, 1957. She had a large mass on the right side of the face involving the floor of the right orbit with narrowing of the palpebral fissure. There were no apparent metastases. The patient was operated on for the fourth time on December 31, 1957, and had a radical right maxillectomy with removal of the floor of the orbit and enucleation of the eye. Within several weeks after the operation, the tumor recurred in the anterior portion of the remaining palate and was again removed.

By April, 1958 the tumor already involved the right nasal cavity and the septum and grew out from the large defect in the palate. It extended into the contralateral maxilla. The patient received radiation therapy with a total tumor dose of 8,000 r in 57 days using a cobalt 60 beam directed to both maxillae. An additional 4,000 r was directed to the exenterated right orbit through a smaller separate field. The tumor receded somewhat for a short time following radiation therapy and then rapidly recurred and involved the left orbit with resultant progressive loss of vision. Because of the imminent blindness of the remaining left eye, it was decided to use radioactive S^{35}.

PROCEDURE AND RESULTS

A tracer dose of 10 mc of S^{35}* was injected intravenously and the uptake was estimated by external scintillation counting of the bremsstrahlung produced by the interaction of the S^{35} beta rays with the surrounding tissue. Studies of the blood, urine and the bone marrow were also performed.

The external counting showed a preferential uptake in the tumor bearing area as against the thigh of from 7 to 12:1 (Fig. 1). Encouraged by this preferential uptake, 1,200 mc was administered in January, 1959. The dosage schedule was as follows: 505 mc on the ninth day, 391 mc on the sixteenth day and 322 mc on the twenty-

* The material was obtained from Abbott Laboratories as sodium sulfate.

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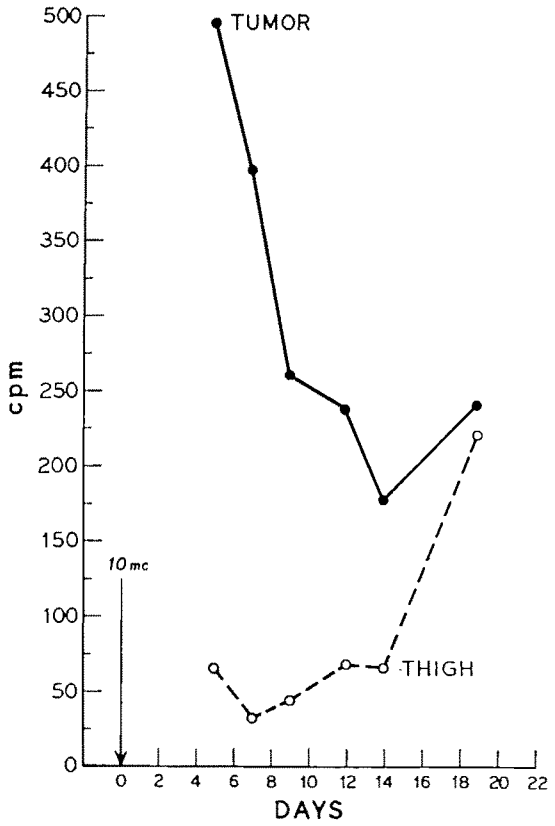


FIG. 1. Count rates obtained with a scintillation detector positioned in contact with the thigh and tumor after a 10 mc tracer dose of S^{35}.

third day of the month. Measurements of blood levels and the amounts excreted in the urine were made at each subsequent 7 day period (Fig. 2). External counting was done again over the tumor, thigh and patella. The results of this counting are shown in Figure 3. The white blood cell and platelet counts fell progressively, starting about 2 weeks after the first dose and reached almost zero 2 weeks later (Fig. 4). The patient received one unit of fresh blood on the eighteenth day after the administration of the first dose of S^{35} because of bleeding from the tumor site. She became febrile up to 103°F. without a definite focus of infection. She was put on antibiotics as well as on 60 mg. prednisone daily. In the seventh week after her first dose of S^{35}, the blood counts returned to normal. The tumor showed no regression but did not seem to grow for about 2 months after the S^{35} administration; then it resumed its rapid growth and the patient became totally blind. Her general condition deteriorated mainly as a result of progressive dysphagia. She died in extreme cachexia on May 26, $4\frac{1}{2}$ months after the administration of S^{35}. The autopsy showed the recurrent tumor penetrating the base of the skull in the middle fossa with displacement and compression of the adjacent brain. There were a few small metastases in the lungs and liver.

COUNTING METHODS AND DOSIMETRY

All external counting was done with a scintillation detector having a 1×1 inch sodium iodide crystal. There was sufficient bremsstrahlung produced by the interaction of the S^{35} beta rays with surrounding tissue to give statistically significant count rates even with the 10 mc tracer dose Blood and urine samples were assayed with a gas flow counter.

Estimates of the dose received by the bone marrow were based upon the measured effective half life of S^{35} in the blood, 0.35 days, and the assumption of uniform distribution of the isotope in the body during the first day following injection. Using standard methods, it can be calculated that the initial injection of 505 mc produced a whole body dose of 180 rads.

Data presented in Figure 4 tend to bear

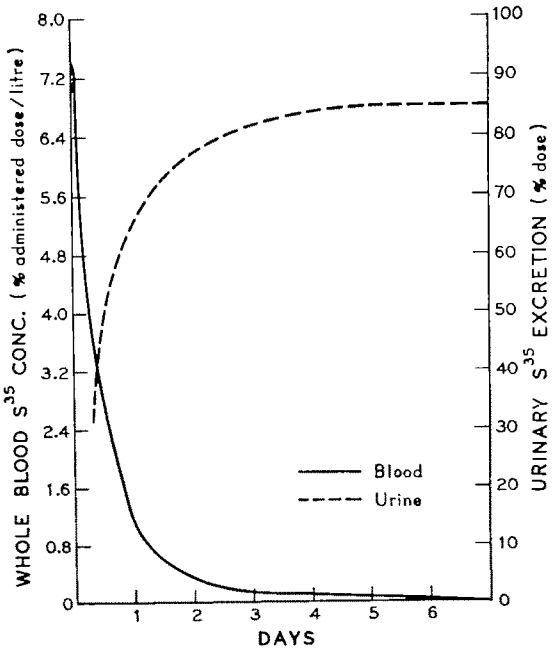


FIG. 2. Concentrations of S^{35} in the blood and urine following a 10 mc tracer dose.

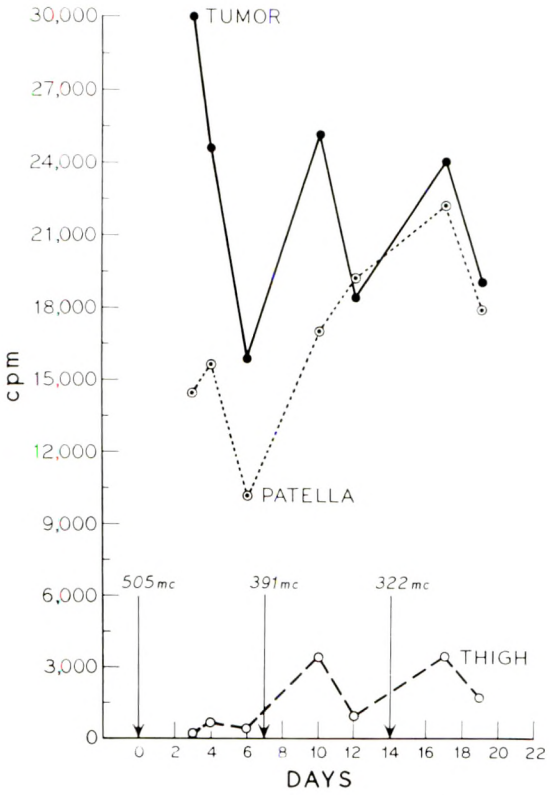


FIG. 3. Count rates obtained with a scintillation detector positioned in contact with the tumor and the patella during the course of treatment with S^{35}.

out this estimate. It can be seen that the white blood cell count began a precipitous fall just 14 days after the first injection. Although it is not possible to relate accurately the slope of the white blood cell curve to the radiation dose, we can say that this clinical picture is not inconsistent with whole body irradiation of this order of magnitude.

Because of the great difficulties in constructing a standard having the same geometry and dose distribution as in the patient, no attempt was made to measure or calculate tumor doses.

With a view towards determining the final distribution of S^{35} in the body, autoradiographs were made from autopsy specimens. The data in Table I are intended to give only a qualitative picture of the final distribution.

Autoradiographs of the tumor occasionally showed higher photographic grain

TABLE I

POSTMORTEM AUTORADIOGRAPHS

Epiglottis***	Muscle*
Thyroid***	Connective Tissue*
Bone***	Spleen*
Tumor**	Pancreas*
Adrenal**	Heart*
Aorta**	Lymph Node*
Lung**	Small Intestine*
Kidney**	Liver*
Skin**	

* slight blackening.
** moderate blackening.
*** marked blackening.

density over fibrotic areas than over cellular areas (Fig. 5, *A* and *B*). In some bone sections, the blackening was more pronounced over areas of markedly depleted marrow than in areas showing more cellularity. We assume that these fibrotic and acellular areas were normal and that the histologic changes were produced by the S^{35} therapy. It should be kept in mind that the distribution of S^{35} in body tissues, as indicated by the data in Table I, is not the same as would be obtained a day or two after administration of the therapeutic dose. It is probable that rapid metabolism of the tumor eliminated the radioactive sulphur faster than normal cartilage so that the distribution changed continuously.

DISCUSSION

In spite of the lack of success in our therapeutic trial, we feel that this case is of interest for the following reasons:

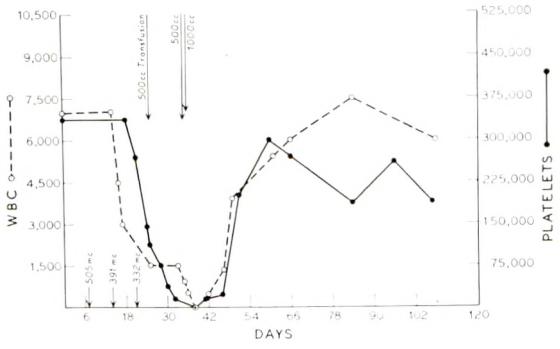


FIG. 4. White blood cell and platelet counts during the course of treatment with S^{35}.

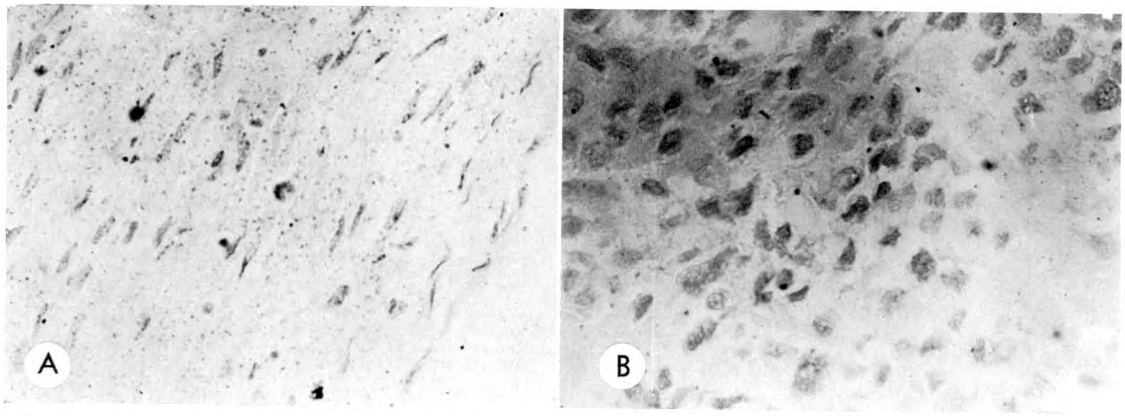


FIG. 5. Autoradiographs made from postmortem sections of the tumor: (*A*) Fibrotic area showing many photographic grains and (*B*) cellular area showing considerably fewer grains. (Both sections ×520.)

1. To our knowledge this is the largest dose of sulphur 35 ever administered. The patient, who weighed only 88 pounds, was given a total dose of 1,218 mc or 30.4 mc per kg.

2. In spite of this seemingly high dose, there was complete recovery of the hematopoietic system in a remarkably short time with relatively modest supportive therapy.

3. Some histologic evidence of a localized destructive effect upon tumor was noted. The postmortem autoradiographs of the tumor tissue compared with the stained slides of the time block showed areas of fibrosis coinciding with increased blackening of the emulsion.

Comparing the course of our patient with the cases treated by Andrews *et al.*[1] and Gottschalk[2] we noted that they obtained better results with greater fractionation of the isotope in spite of a lesser total dose. Being completely ignorant as to the rate of the cell division in the tumor, we might have had better results by extending the treatment over a period of 6 to 8 weeks as practiced with external beam radiation therapy. The greater over-all time of the administration of the isotope might have permitted some recovery of the hematopoietic system before reaching the point of severe depression. It is also possible that in cases with good response, multiple courses could be applied.

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The authors would like to express their appreciation to Mr. Edward Siegel for his invaluable assistance in preparing the autoradiographs and assaying the blood and urine levels of radioactivity. Also, we thank Mr. R. J. Schulz for his valuable criticism and editorial assistance.

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REFRIGERATION AND IRRADIATION: AIR COOLING OF THE SKIN FIELD DURING ELECTRON BEAM THERAPY*

By EDWIN J. LIEBNER, M.D.
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IN A previous paper, the skin sparing effect of regional cooling of the irradiated skin field was reported.[1] At that time conventional roentgen rays, 300 kv., half value layer 4 mm. Cu, were used. Cold water was circulated through a lucite cone and application was made to the relatively large, flat skin surfaces of the lower abdomen and buttocks. When using a water cooling source and a rigid flat cone, it is difficult to apply it to irregular surfaces; *e.g.*, chest, head, or neck contours. It was thought that an air jet stream could be developed as the cooling agent. We were particularly interested in combining it with electron beam therapy for many head and neck lesions since the skin in many of these cases has been observed to have rather marked radiation changes. The purpose of this paper is to cite the use of air for cooling during irradiation, and report the observations made when the skin field temperature is lowered during electron beam therapy. I believe that this has never been used previously, and interested readers are referred to the historical comments in the earlier paper.[2]

METHOD

The cooling apparatus consisted of a ¾ ton compressor (Frigidaire) which circulates a compressed gas, Freon 12. This compressor was connected to a three pass chilling coil (Fig. 1). To one of the ends of the chilling coil, compressed air was added. The air flow was measured through a Fischer-Porter flow rater and had a maximum flow of 11 cubic feet per minute. The cooled compressed air made exit from the other end of the chilling tank by means of 2 insulated hoses, each 48″ long. Each hose was attached to a hollow vertical lucite tube sealed at the other end. The tube measured 15 cm. in length, with an inner diameter of 2.0 cm. These tubes were attached to the end of the lucite treatment cone, opposite each other. A 0.2 cm. vertical slit made diagonally through the entire length of the tube gave a jet or stream of cooled air directed from both sides of the treatment portal onto the skin (Fig. 2).

In order to obtain multiple temperature readings almost simultaneously, 5 thermocouples were attached to the skin of the irradiated field. The thermocouples are copper, constantan elements. An additional reference thermocouple was placed in a Dewar flask (thermos) containing ice chips and water. The thermocouples were attached to an electronic potentiometer (Minneapolis Honeywell-Brown Instrument) which had a range of voltage up to 70 millivolts.[2] Temperature readings were made 1, 3, 5, 7 and 10 minutes after the cooled air jet was applied.

The electron beam of the 23 mev. betatron (Allis-Chalmers) was used. The electrons were extracted at 10 mev., 15 mev., and 21 mev., depending on the nature and the depth of the lesion to be treated; *e.g.*, cervical metastatic lymph nodes, carcinoma of larynx or carcinoma of the tonsil.

RESULTS

From January, 1962 to July, 1962 we have treated 35 patients with combined electron beam and lowered temperature of the irradiated skin field. At first the skin was cooled by simply applying an ice bag for 15 minutes prior to treatment, while a cooling coil was being constructed for the

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Work supported by a grant from Illinois Division, American Cancer Society.

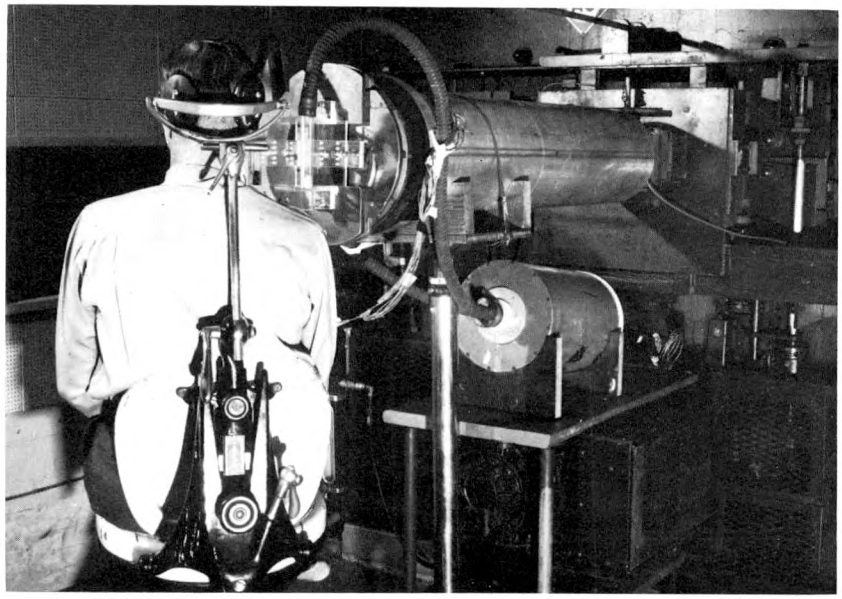


FIG. 1. The air cooling apparatus adapted to the collimating treatment cone of a 23 mev. betatron (Allis-Chalmers). Below to the right is a $\frac{3}{4}$ ton compressor which circulates Freon 12. Intermediate in position is the chilling coil tank. Inferiorly between the patient and cooling apparatus one can see the compressor air hose source.

air jet method. When ice bags were used for cooling, there was a great deal of variation in the effectiveness of cooling achieved over the area applied. The patients had to hold the bag in place and, in so doing, the bag was often held unevenly with pressure or snugness against the skin field. Figure 5 shows the disparity in application when the ice bag was held on the side of the face and neck. There was adequate cooling in the superior portion of the field, but poor contact inferiorly where the usual marked skin changes occurred. Another disadvantage of the ice bag method is that it has to be removed at the time of treatment, since too much electron scatter and absorption would occur. Thus, maximum cooling is not maintained at the time of irradiation. A plastic chemical cooling bag (Kwik-Kold) was studied on one patient (No. 11). This bag when crushed allows the chemicals to mix, producing cooling. The cooling obtained with Kwik-Kold equaled that of an ordinary ice bag and its effect was maintained for at least 15 minutes while applied. However, since these chemical bags are moderately costly and may not be repeatedly used, we abandoned this type of cooling entirely. Table 1, column 3, briefly summarizes thermocouple skin temperatures in Fahrenheit readings made over 5 points of the skin field when ice bags were applied.

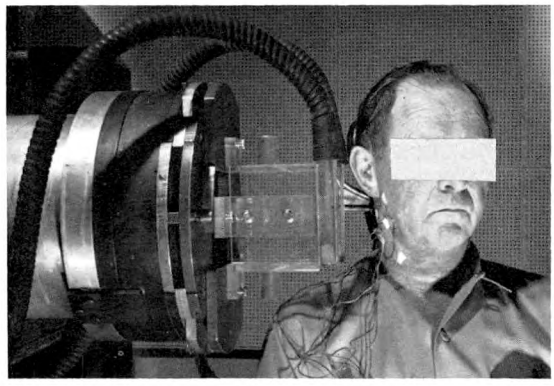


FIG. 2. Anterior view of air jet cones attached to the distal end of the treatment portal. Thermocouples are in place for temperature study. During actual treatment, the patient is nearer the treatment air jet cone. See text.

The air jet stream cooling of the skin gave a more uniform reading of the thermocouples distributed over the irradiated

field. Table 1, column 4, presents some of the readings obtained in 16 cases studied. The great advantages of air cooling are that no absorber is interposed between the radiation and the skin surface, and cooling is maintained throughout the radiation treatment. It was noted that approximately 3 minutes of air cooling prior to treatment was necessary to achieve skin temperature equilibrium. This is similar to the water cooled cone that was reported in the previous study.[1,2] The temperature of the air cooled source reaching the vertical plastic jet columns for distribution over the skin field was −3°C. or 26.6°F. With the air jet stream at the edge of two sides of the treatment field, the center thermocouple gave a mean of 58°F. Of course, there were lower skin readings, particularly when the thermocouple was directly opposite the jet source and in opposition (Fig. 2). Thermocouple readings were made in the inner buccal mucosa of 5 patients whose outer skin was air cooled. While the mean skin temperature was 58°F., the buccal mean temperature was 94°F. Thus, the effective cooling of the air jet stream is superficially confined to the dermis.

The skin temperature readings obtained prior to any cooling ranged from 86 to 90°F. in 4 patients (mean 88°F.). Thus, the effective lowering of the skin temperature accomplished by the air cooled method is a mean 30 degrees. This is for an average area of 9×11 cm. (Table 1, column 3). There has been no discomfort at these temperatures. The patients find it extremely comfortable on warm, humid days.

DISCUSSION

Zatz *et al.*[5] have reported that electron beam doses of 5,700 rads delivered in 5 weeks to a 10×12 cm. skin field regularly produced severe, dry reaction with a wet reaction in a large portion of the field. Veraguth[4] has seen desquamating skin reaction, usually occurring after 6,000 to 7,000 r, lasting over 2 to 3 weeks. We have also seen severe moist desquamation at about the 7,000 to 7,500 r level, especially if 1,500 r was given per week (300 r/day).[3] Figures 3 and 4 show the usual skin responses that we were accustomed to seeing prior to any cooling.

With air cooled lowering of the skin temperature, the irradiated skin field has shown some evidence of protection with lessening of the marked changes shown. Erythema appears later (4,000 r) and evolves slowly to a dry scaling reaction at the higher doses (8,000 r). The moist desquamation is less commonly seen with the cooling method. When one reduces the usual dose rate from 300 r daily to 200–250 r daily, thereby extending the treatment period one more week, better skin protection is seen. Figures



FIG. 3. M. M., 51 WM, after 4,500 r and beginning the 4th week of treatment. Metastatic lymph nodes from previously operated carcinoma of the left lateral tongue. Patient received 7,900 r in 35 treatments and 6 weeks. Usual marked skin changes were noted with cancericidal dosages using electron beam therapy and no cooling.

Table I

Patient	Diagnosis	Field Size (cm.)	5 Thermocouples over Skin Field F.°		Remarks
			Ice Bag Cooling	Air Jet Cooling	
1. T.B. 86 WM	Carcinoma of left true cord	5×5	68, 59, 62, 50, 61	62, 58, 58, 56, 58	7,075 r, 7 wk., 35 treatments, 200 r/day, dry erythema
2. W.O. 58 WM	Carcinoma of right tonsil and tongue	10×12	81, 72, 76, 60, 86	66, 60, 61, 56, 64	8,175 r, 6 wk., 33 treatments, 225–300 r/day; dry, scaling erythema
3. C.G. 58 WM	Carcinoma of right tonsil and neck	10×12	67, 53, 65, 56, 86	73, 61, 63, 60, 77	7,325 r, 7 wk., 32 treatments, 225–300 r/day; dry, scaling erythema
4. R.H. 62 WM	Carcinoma of right tonsil, palate and tongue	10×12	76, 66, 79, 60, 82	70, 53, 57, 56, 54	8,850 r, 7 wk., 34 treatments 250–300 r/day; dry, scaling erythema
5. A.S. 72 WF	Carcinoma of buccal mucosa	9×9	68, 67, 57, 61, 67	56, 53, 54, 62, 50	7,750 r, 6 wk., 30 treatments 225–300 r/day; mild erythema
6. T.B. 54 NM	Carcinoma of right epiglottis and aryepiglottic fold	9×10	62, 57, 58, 58, 66	68, 60, 64, 52, 68	Previous thermal injury. 7,050 r, 4½ wk., 28 treatments, 250–300 r/day; markedly erythematous
7. O.O. 83 WM	Carcinoma of left posterior tongue	10×11	65, 56, 78, 47, 63	46, 56, 60, 61, 60	Therapy discontinued after 3,000 r; terminal
8. C.T. 60 WM	Carcinoma of left maxillary sinus	10×11	62, 73, 52, 72, 57	68, 60, 58, 62, 70	8,575 r, 54 da., 36 treatments, 200–300 r/day; moderate erythema
9. G.S. 19 WF	Carcinoma of right true cord	5×5		58, 62, 56, 60, 60	7,000 r, 7 wk., 200 r/day; dry, scaly erythema
10. R.G. 72 WF	Carcinoma of left posterior tongue	9×11		66, 62, 66, 58, 66	7,000 r, 6 wk., 32 treatments, 200–250 r/day; moderate erythema
11. H.G. 57 WM	Carcinoma of right tonsil and neck	10×12	62, 62, 64, 60, 63 59, 65, 63, 79, 80 Kwik-Kold bag	58, 52, 58, 54, 63	7,650 r, 6 wk., 28 treatments, 250–300 r/day; dry erythema
12. I.R. 74 WM	Carcinoma of left palate, tonsil and neck	9×11		74, 66, 75, 56, 56	Cerebral hemorrhage; treatment incomplete; 4,500 r; mild erythema
13. G.H. 57 WM	Carcinoma of right tonsil and neck	9×12		68, 54, 66, 70, 70	6,750 r, 40 da., 30 treatments, 225 r/day; mild, scaly, dry erythema

Table I (*Continued*)

Patient	Diagnosis	Field Size (cm.)	5 Thermocouples over Skin Field F.°		Remarks
			Ice Bag Cooling	Air Jet Cooling	
14. E.K. 53 WM	Carcinoma of left palate, tonsil and tongue	10×13 9×12		60, 64, 60, 62, 54	7,800 r, 6 wk., 26 treatments, 300 r/day; slight scaling, dry erythema
15. P.B. 61 WF	Right metastatic neck (carcinoma of right antrum)	11×12		56, 58, 54, 63, 59	7,800 r, 6 wk., 26 treatments, 300 r/day; dry erythema
16. W.G. 84 WM	Laryngectomy site and neck; recurrence after surgery	10×10		56, 60, 52, 56, 56	7,800 r, 6 wk., 26 treatments, 300 r/day; erythema, late desquamation



Fig. 4. A. H., 71 WM. Carcinoma of right tonsil. Marked moist desquamation. Patient received 7,900 r in 34 treatments and 6 weeks with no cooling. Photograph was made 3 days before the completion of the course of treatment.

6 through 11, inclusive, show some of the usual responses that we have observed with skin cooling.

This preliminary study does not have the control features of our earlier experiment,[2] but in this instance we are concerned with the application of air as a means of cooling and we feel that it has a definite advantage. Irregular contours can easily be cooled and so maintained while the radiation is given.

The skin sparing that was seen in this study, although only slight to moderate, is encouraging. One has to realize that the cooling apparatus was assembled out of discarded materials and only the temperature range it could produce was studied. The skin temperature lowering from 88° to 58°F. (mean) for the small area of the body treated was tolerated with no objective or symptomatic effects. The mild protective changes seen are probably occurring in the upper range where clinical effects are just barely noticeable. If this crude equipment achieved these temperatures and responses, certainly better designed equipment can achieve better air jet stream cooling. There is more to be hoped for, if the skin temperature could be lowered to a range of 38° to 44°F.

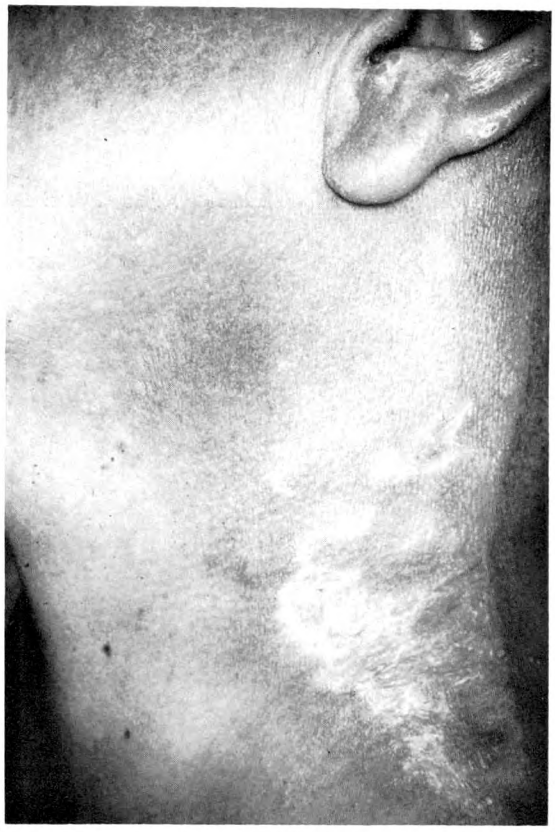


Fig. 5. B. G., 48 WF. Carcinoma of left soft palate. A 10×12 cm. treatment portal was employed. Ice bag cooling was used on the left side of face and neck. Uneven application resulted in skin sparing in superior portion and marked skin changes inferiorly where cooling contact was poor. Patient received 7,250 r in 33 treatments and $6\frac{1}{2}$ weeks. Photograph was made 2 weeks after treatment.

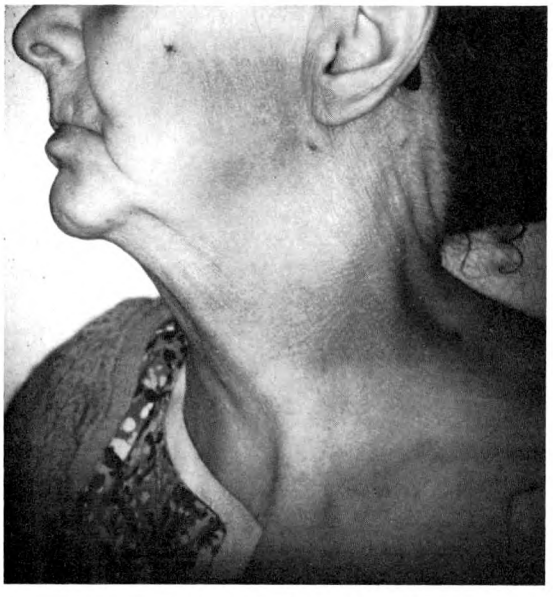


Fig. 6. Patient No. 10. R. G., 72 WF. Carcinoma of the left posterior base of tongue. Moderate erythema is seen. The patient received 7,000 r in 32 treatments and 6 weeks. Photograph was made the last week of treatment.



Fig. 7. Patient No. 11. H. G., 57 WM. Carcinoma of the right tonsil. Marked erythema is seen. The patient received 7,650 r in 28 treatments and 6 weeks. Photograph was made the last day of treatment.



Fig. 8. Patient No. 5. A. S., 72 WF. Carcinoma of the right buccal mucosa. Moderate erythema is seen. The patient received 7,750 r in 30 treatments and 6 weeks. Photograph was made last day of treatment.



FIG. 9. Patient No. 4. R. H., 62 WM. Advanced carcinoma of the right tonsillar area. Dry, scaly erythema is seen. The patient received 8,850 r in 34 treatments and 7 weeks. Photograph was made the last week of treatment.

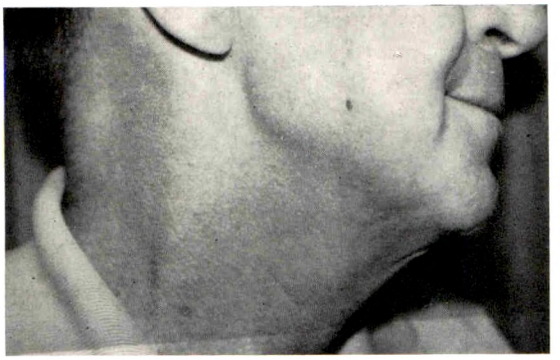


FIG. 10. Patient No. 3. C. G., 58 WM. Carcinoma of the right tonsil. Residual erythema is seen 2 weeks after treatment. The patient received 7,325 r in 32 treatments and 7 weeks.

SUMMARY AND CONCLUSIONS

Various observers have commented that the electron beam has very little skin sparing effect compared to megavoltage roentgen rays or to orthovoltage roentgen rays when the relative biologic effectiveness is taken into consideration. However, the electron beam because of its physical properties in deeper tissues has more favorable application to lesions about the head and neck. If the skin reaction of the electron beam can be lessened while the tumor dose is maintained, this modality of therapy would further increase in usefulness and popularity.

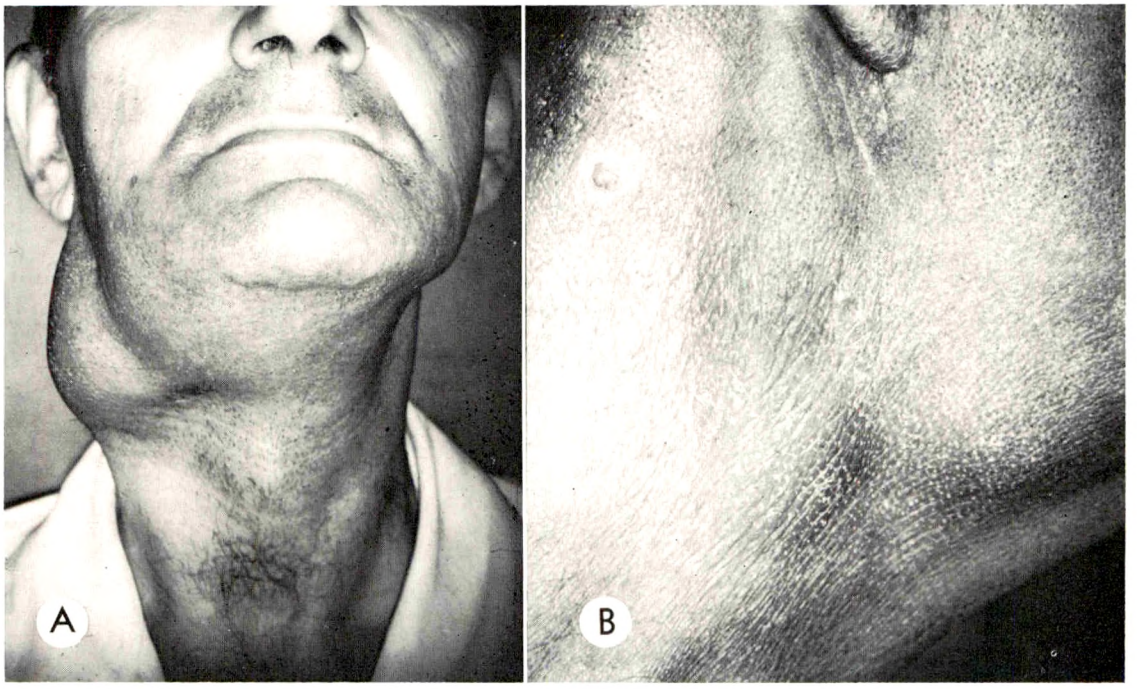


FIG. 11. G. S., 52 WM. (*A*) Pre-treatment photograph showing undifferentiated carcinoma metastatic to the right upper cervical lymph nodes. (*B*) Post-treatment photograph showing moderate scaly erythema 4 days after treatment. The patient received 8,300 r in 32 treatments and 7 weeks.

An air cooling method of the irradiated skin field would be ideal since: (1) cooling can be maintained throughout the treatment, (2) no material is interposed to change the electron scatter or absorption, and (3) irregular contours can easily be cooled.

From available materials, a cooling apparatus was designed which lowered the skin temperature to a mean 58°F. Ice bag and air cooling was compared. The air jet stream cooling was studied in 35 patients and representative examples are given. There was mild to moderate protection of the irradiated skin field and moist desquamation was less commonly seen. Better designed cooling equipment capable of lowering the skin field temperature to a 38° to 44°F. range should give even better results.

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ISOINTENSITY PATTERNS FROM RADIOACTIVE COLLOIDAL GOLD IN SEROUS CAVITIES*

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WHEN the distribution of radiation about a patient containing instilled radioactive isotope is known, the precautionary measures established for nursing and other personnel can be of an informed and realistic type.

The dose rates in milliroentgens per hour were established in the vicinity of patients who contained radioactive colloidal gold in either the pleural cavity or in the peritoneal cavity.

The distribution of the gold in the serous cavity was checked by the radioautographic and roentgenographic combined technique described by Hidalgo, Burns and Nieset.[1] This consists of obtaining a radioautograph and then having a superimposed roentgen exposure made of the abdomen or chest of the patient. This was generally done approximately 1 hour after the isotope had been injected, in order for the distribution to be as optimal as possible. Such a combined autoradiograph and roentgenogram is shown in Figure 1. In this instance, the patient had had 100 mc of Au^{198} placed in the right pleural space.

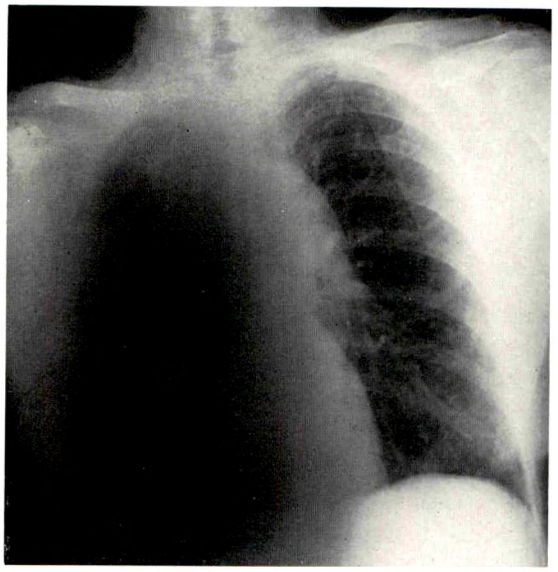


FIG. 1. Radioautograph and superimposed chest roentgenogram after instillation of 100 mc of Au^{198} into the right pleural space.

At the time of the measurements, each patient was placed supine in a conventional hospital bed and the bed was positioned in the middle of the room. This relationship of bed to room permitted one to check the isointensity patterns in a plane completely around the patient, rather than only in a hemicircle. A complete isointensity pattern gives a better idea of the absorption of the radiation by the patient, particularly when a single pleural cavity is treated.

All measurements were made with a Tracerlab Model SUIH radiation survey meter. This instrument was calibrated prior to each set of determinations with a standard radium source and the instrument was checked again after the measurements were obtained. The calibration of the meter remained constant.

All readings were obtained at the midplane of the patient's body. This averaged a distance of approximately 36 inches above the floor. Multiple recordings were made at different distances from the central location of the pool of isotope in the patient. These initial measurements were followed by others when decay had reduced the dose to either 50 mc, or a multiple of 50 mc. From points of equal radiation intensity, isointensity curves were plotted.

Figure 2 shows the isointensity distribution around a patient in whom 150 mc of radioactive colloidal gold was injected intraperitoneally. It can be noted that at dis-

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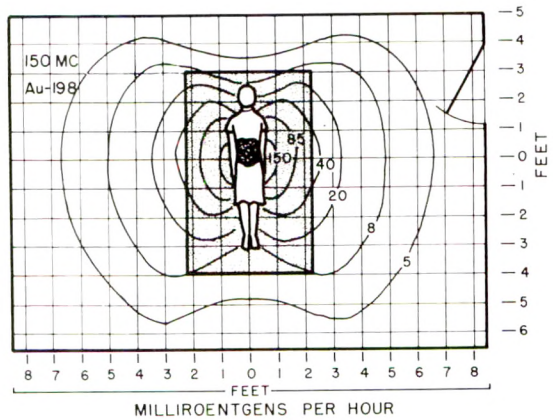


FIG. 2. Isointensity distribution pattern around a patient who has had 150 mc of Au^{198} placed into the peritoneal cavity.

tances greater than 2 feet, the mr/hr. values on the lateral aspects of the patient tend to obey the inverse square law. However, around the head and feet, they do not. This is to be expected because of the shielding effect of the greater amount of body tissue. As a consequence, the geometric pattern is a changing one for each isointensity curve.

During decay, the pattern of distribution around the patient remains the same, but of course the dose rate diminishes. Figure 3, *A* and *B* shows such curves for an intraperitoneal injection at both the 100 mc (*A*) and the 50 mc (*B*) levels.

When radioactive colloidal gold is placed in one pleural cavity, there is a marked difference in the contours of the isointensity curves on each side of the patient. Here, the asymmetry is secondary to the absorption by the contralateral hemithorax. Figure 4, *A* and *B* shows the curves for a unilateral pleural cavity injection at both the 100 mc (*A*) and 50 mc (*B*) dose levels.

By the use of such graphs one can readily determine the instructions that must be given to nursing personnel during the total period of patient hospitalization. It is evident, also, that in the instance of a pleural space injection, the bed of the patient should be so positioned that the treated hemithorax is near an outside wall. This assures that the nursing care of the patient will always be given in an irradiated zone of less intensity. For instance, at the edge of the bed, the mr/hr. value on the untreated side is but half that in the same position of the treated side.

Utilizing these isointensity curves, one can approximate the dose received by the physician and other attending personnel during the actual period of injection.

Visitors should be restricted to nonpregnant adults and they should be advised to stay several feet from the bed and preferably at its end. As pointed out by Nurnberger,[2] a reasonable maximum permissible exposure for a visitor is 500 mr since the probability of repeat exposures to the same individual in the same year is extremely low; therefore, exaggerated precautions

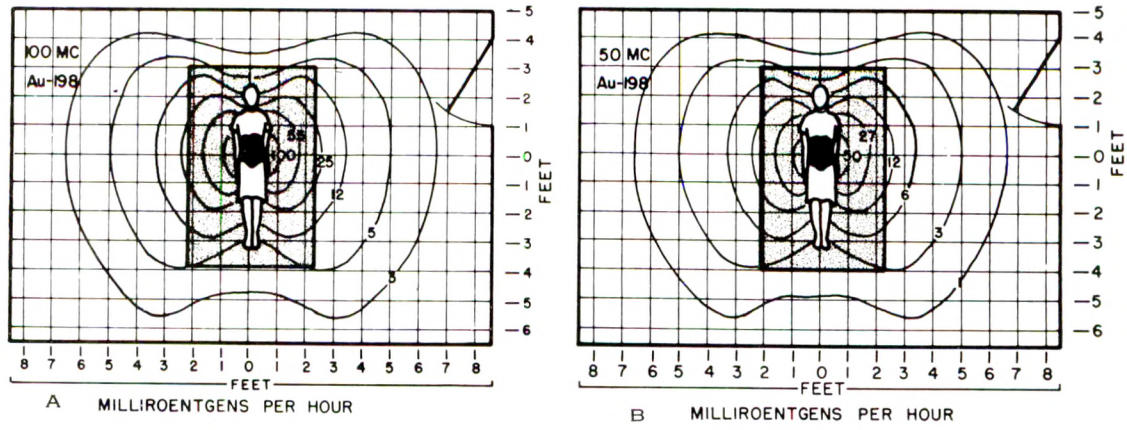


FIG. 3. (*A* and *B*) Decay patterns for comparison with Figure 2.

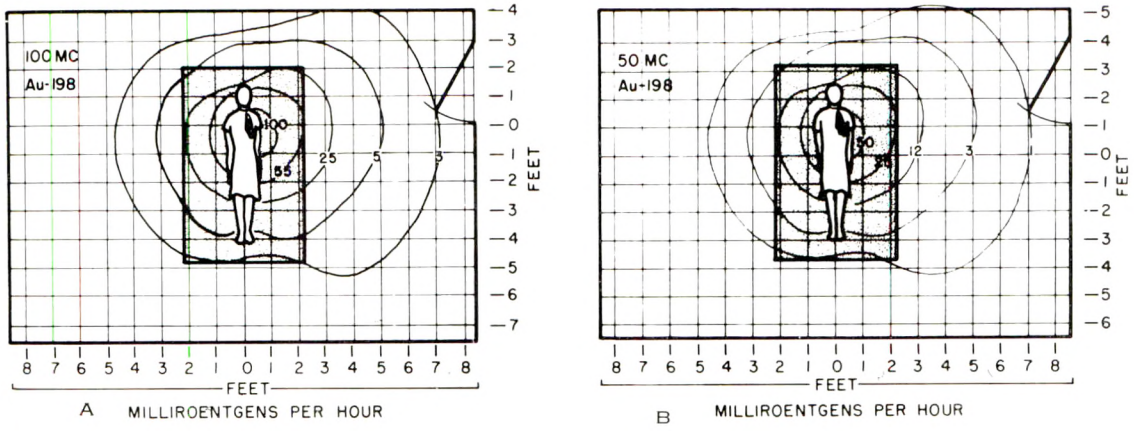


FIG. 4. The isointensity patterns after treatment of one pleural cavity are asymmetric. These are shown for injections of 100 mc (*A*) and 50 mc (*B*).

need not be taken. Reference to Figure 2 indicates that a visitor to a patient containing 150 mc of Au^{198} in the peritoneal cavity, if 2 feet away from the end of the bed, could be present for 100 hours, even neglecting decay.

SUMMARY

Isointensity patterns for the distribution of radiation around patients treated with radioactive colloidal gold were obtained. These patients had had the isotope instilled either into a pleural cavity or into the peritoneal cavity. Diagrams indicating the dose in mr/hr. around a patient in a conventional hospital bed are presented.

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A PHYSICAL STUDY OF A STRONTIUM 90 β-RAY APPLICATOR*

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STRONTIUM 90 applicators have been used for the treatment of lesions of the eye for a number of years. Although a relatively large volume of literature exists regarding the central axis depth dose, relatively little has been published concerning the complete isodose curves. Particularly absent are efforts to control the field size and to study its effects on depth dose and isodose distributions. In most cases the same applicator has been used regardless of the size of the lesion so that the dose to the lens of the eye may be much larger than necessary.

Loevinger[7] has described the use of extrapolation chambers for calibration of beta sources and has also discussed the theoretical aspects in detail.[8] Haybittle[3,4] and Krohmer[5] have used ionization chambers and extrapolation chambers to obtain the central axis depth dose. Freitag *et al.*,[2] and Tochilin and Golden[11] have used photographic emulsions while Walinder[13] has used a scintillation crystal probe for this same purpose. McTaggart *et al.*[9] have used photographic films to plot isodose curves for tissue.

In this study an extrapolation chamber was used to obtain the surface dose rate and central axis depth dose. Isodose curves were obtained from film measurements. The effective spot size was determined by film and so also was the size of the active area. Lead sheeting, 0.022 inch thick, was used as a field shaping material. A number of field limiting diaphragms were made up and the dosage characteristics studied, both with film and with the extrapolation chamber.

The β-ray applicator used in this study was made by Tracerlab. The Sr^{90} is deposited on a flat surface to form a circular area and this is covered with a thin window made of 0.002 inch of stainless steel and 0.010 inch of Al.[12]

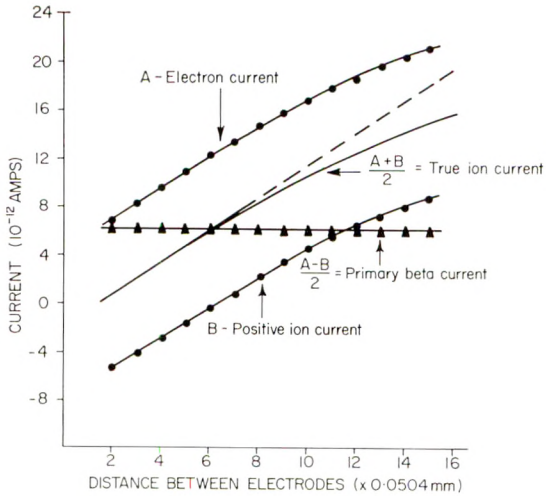


FIG. 1. Extrapolation chamber data showing variation of ion current with the electrode separation. Shown are positive and negative ion currents and true ion current and primary beta current.

SURFACE DOSE RATE

An extrapolation chamber, of the general type first devised by Failla,[1] was constructed to make measurements on this applicator. Such chambers and their operation have been described in detail elsewhere.[7]

The data required for the surface dose rate measurement are shown in Figure 1, where the positive and negative ion currents are plotted against plate separation. The true ion current is given by the average of these and is indicated by the heavy curve. The initial slope of this curve gives the surface dose rate as 32.69 e.s.u. per sec. per $cm.^3$ of air at 0° C. and 760 mm. Hg.

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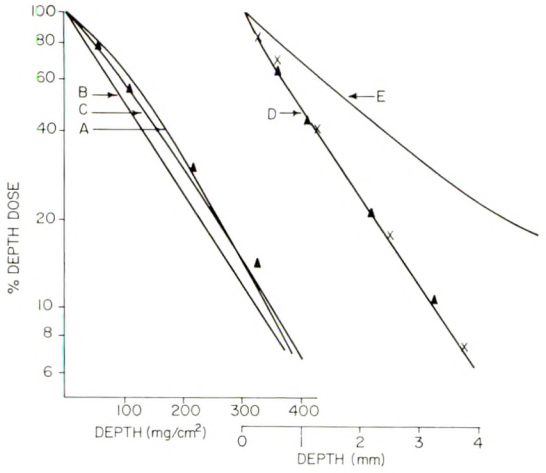


FIG. 2. Graphs of the percentage depth dose data obtained from extrapolation chamber measurements using polystyrene film base material and aluminum as phantom material. On the right hand side are shown the percentage depth dose data corrected to unit density.

Using a conversion of $\bar{f}=0.987$[10] (0.877 $\times 1.126$), this gives an absorbed dose rate in soft tissue of 32.27 rads/sec.

Half the difference between the positive and negative ion currents is the current due to the beta particles themselves. Figure 1 shows that this beta current is independent of plate separation indicating that for these separations all electrons cross the gap.

CENTRAL AXIS DEPTH DOSE

Figure 2 gives measurements of central axis depth dose as obtained in a number of different ways. Curve A was obtained by placing a stack of single emulsion films below the applicator, and the depth dose determined from optical density measurements. To obtain curve B the dose, as measured by the extrapolation chamber, was determined as a function of the thickness of the polystyrene absorbers ($\rho=1.04$ gm./cm.^{3}) placed between the applicator and the detector. The disagreement between the curves A and B was thought at least partly due to the number of inherent inaccuracies of film dosimetry such as nonlinear response, energy dependence and nonuniform development. Hence, depth dose measurements were made with the extrapolation chamber and film base material ($\rho=1.25$ gm./cm.^{2}) as phantom material. The results are shown by curve C. The disagreement between the curves C and B is greater than the experimental error and the question arises as to which is the correct measurement and why is there disagreement? In both cases, the depth is shown in mg./cm.^{2} but in the case of curve C, the actual depth below the applicator in centimeters is less than the depth expressed in gm./cm.^{2}. Thus, for example, although a depth of 200 mg./cm.^{2} in case B corresponds to a depth of nearly 2.00 mm. (actually 1.92 mm.) in case C, the depth is only 1.6 mm. so that a higher dose is obtained. The triangles in Figure 2 represent depth dose measurements obtained by using aluminum as a phantom material ($\rho=2.7$ gm./cm.^{3}). These show higher values of depth dose, supporting this reasoning. To show positively that this geometric error is the explanation, the following experiments were performed.

The distance in centimeters between the applicator and the extrapolation chamber was accurately controlled by the carriage of a travelling microscope and made equal in each case to the thickness of the absorber expressed in gm./cm.^{2}. Measurements made in this way with absorbers of polystyrene, film base material and aluminum all gave good agreement as seen by curve D of Figure 2. This graph is also in close agreement with curve B in which the density of the absorber (polystyrene) is very close to unity. To explore these ideas further, the depth dose in air was measured as a function of distance and this is shown as curve E. The fall-off with distance, in air, which may be taken essentially as a geometric factor, can be seen to be very considerable. Curve D shows that the material of the absorbers used in the depth dose measurements is not important provided the depths correspond to what they would be if unit density material were used. Further conclusion from these experiments can be drawn that in case an extrapolation chamber is not available, film dosimetry can be

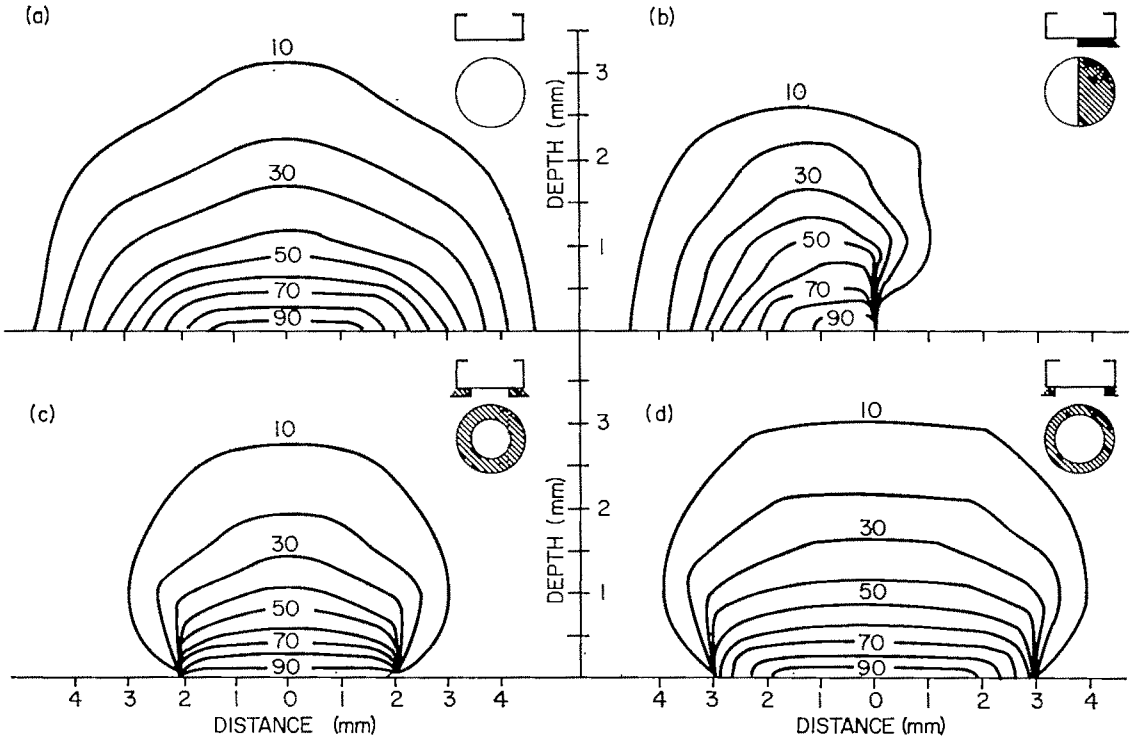


FIG. 3. Isodose curves in tissue obtained by using films and central axis depth dose data. (*a*) Unlimited applicator; (*b*) half covered applicator; (*c*) field limited to 4 mm. diameter and (*d*) field limited to 6 mm. diameter.

used for depth dose measurements provided spacers are used to simulate unit density material.

ISODOSE CURVES

To obtain isodose curves the films were used exposed end-on between two lucite blocks. An enlargement by a factor of 10 was made and the enlargement examined with a densitometer. Contours of equal density were traced and by referring to the central axis depth dose described above, the absolute values of the isodose lines were assigned. Isodose curves obtained this way are shown in Figure 3*a* where the diameter of the field, as judged between the 50 per cent contours, can be seen to be 6 mm. while the 10 per cent contours extend to a diameter of 9.5 mm. This indicates clearly that the irradiated region extends well beyond the quoted spot size of 6 mm. It is thus strongly felt that some field limiting device should be provided for use with the applicator. In selecting the field limiting material, the following considerations were taken into account. The amount of material should be sufficient to cut the beta dose to a small value. If low atomic number material were used, bremsstrahlung radiation would be minimized but the aperture would be physically thick and the source would be held at a large distance from the surface. It was found that sheet lead of 0.022 inch thickness was suitable. In agreement with Haybittle[5] it was found that the bremsstrahlung radiation produced in the lead contributed less than 1 per cent of the beta dose (Fig. 4).

Figure 3, *b*, *c* and *d* shows isodose curves obtained for three field limiting diaphragms. For Fig. 3 *b* one half of the applicator is covered leaving a semicircular exposed area. Figure 3, *c* and *d* shows the effect of reducing the field diameter to 4 mm. and 6 mm. The sharp field edges pro-

duced are noteworthy and are much superior to the fuzzy edges produced by the commercial applicator. It must be pointed out that the use of a field limiting diaphragm reduces the dose rate and the depth dose values. This is discussed below.

VARIATION OF SURFACE DOSE RATE WITH DIAPHRAGM SIZE

The skin surface dose rates for a number of diaphragm sizes were measured with the extrapolation chamber. The results are shown in Figure 4. The dose rate increases with field diameter almost linearly up to 4 mm. and then approaches an asymptotic value at about 8 mm. A measurement was made with the applicator completely covered corresponding to zero area giving the response due to bremsstrahlung radiation alone.

The dose rate for the largest aperture is 25.5 rads/sec. This is 79 per cent of the contact surface dose rate of 32.27 rads/sec. The reduction is due to the diaphragm acting as a 0.022 inch spacer between the applicator and ion chamber. The central axis depth doses are also affected by diaphragm size and the results as obtained with the extrapolation chamber are plotted in Figure 5. The percentage depth dose increases as the diameter increases. This is more clearly indicated by the insert which shows the percentage depth dose for three different depths plotted against field diameter.

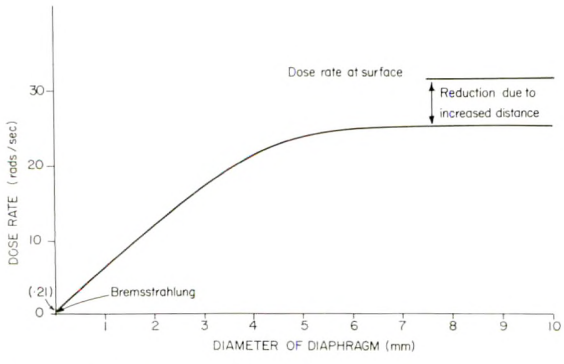


Fig. 4. Diagram showing variation of surface dose rate with diameter of the field limiting diaphragm.

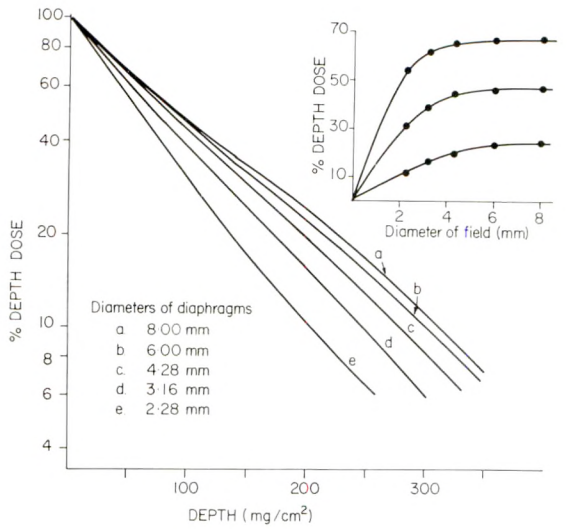


Fig. 5. Diagram showing variation of the percentage depth dose with the diameter of the field. The insert shows a cross plot of percentage depth dose against diameter of field for depths of 0.5 mm., 1.00 mm. and 2.00 mm.

SUMMARY AND CONCLUSIONS

Depth dose data and isodose curves have been obtained for an Sr^{90} eye applicator both for surface application and for the use of field limiting diaphragms made of thin lead sheeting. A few diaphragm shapes have been studied but any shape desired

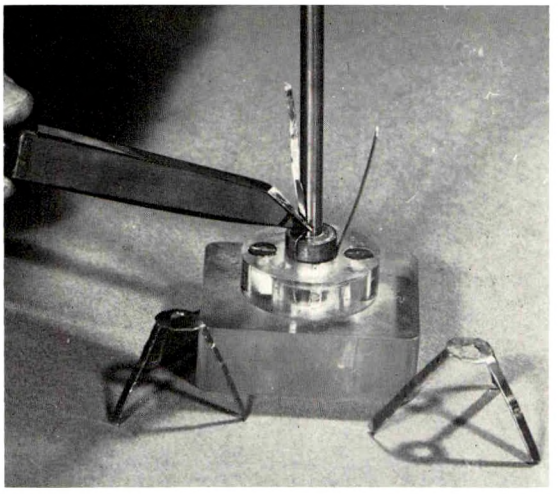


Fig. 6. Photograph showing the use of a jig for mounting the field limiting diaphragms on to the applicator. The jig centers the diaphragm and provides protection to the fingers. In the foreground are shown two additional field limiting diaphragms.

can be readily fabricated, using a pair of scissors and a razor blade. Care must be taken with alignment. Figure 6 shows a diaphragm being attached to the applicator, using a specially constructed lucite jig. This jig serves the dual purpose of centering the diaphragm and affording protection to the fingers. In Figure 6 the clamping straps are being bent around the back of the applicator to hold the diaphragm in place. Other devices for attaching the diaphragm could be designed but the method described has been found to be extremely simple.

Isodose curves for special shapes can be obtained rather easily using a single end-on exposed film. Central axis depth dose data could be selected from Figure 5, and using this in combination with isodensity curves from the film, the complete isodose lines can be plotted.

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SCATTERED RADIATION AND NEUTRON FLUX MEASUREMENTS AROUND A 35 MEV. BETATRON INSTALLATION*

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THIS paper deals with the results of a protection survey in the areas adjacent to the recently installed 35 mev. betatron unit.

The betatron occupies the center of a room 25 feet long, 18 feet wide and 12 feet high (Fig. 1). The walls of the room are of concrete of the following thicknesses: Wall B—4 feet 10 inches concrete, Wall D—3 feet 4 inches concrete, Walls A and C, perpendicular to the direction of the beam, are of Baryte concrete, 4 feet 10 inches thick (Fig. 2). The absorption coefficient of Baryte concrete is approximately twice that of the ordinary concrete, its specific weight being 3.5 gm./cm.^{3} In Wall D above the control panel, there is a glass tank filled with approximately 200 gallons of water. This tank serves as an observation window. The roof adjacent to the machine room is inaccessible to personnel and signs are posted warning against radiation, which also originates from cobalt and cesium units in our department. There is no occupational structure below the floor of the betatron room.

Measurements were taken outside the betatron room for roentgen rays at 35 mev. and electrons at the maximum energy of 35 mev. Maximum field sizes were used at the regular treatment distances of 100 cm. for roentgen rays and 110 cm. for electrons. A lucite phantom, 30×30×30 cm., specific gravity 1.18 gm./cm.^{3}, was used for scattered radiation. This phantom was replaced by a mix-D phantom of identical dimensions for neutron measurements.

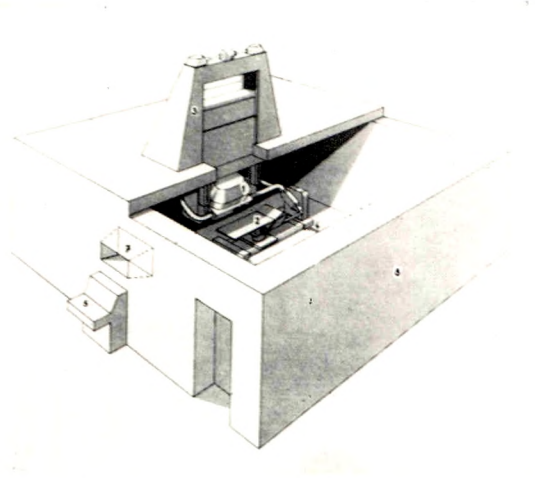


FIG. 1. Diagram of the 35 mev. betatron unit. (1) Betatron; (2) treatment table; (3) elevating mechanism; (4) guide rails for treatment table; (5) operating panel; (7) window; and (8) Baryte concrete wall.

SCATTERED RADIATION

Scattered radiation in the rooms adjacent to the betatron room was measured with the Nuclear Chicago Portable Survey Meter Model 2612. This battery operated instrument employs a Geiger Müller counter and a count-rate circuit to measure beta and gamma radiation of low and medium intensities. The instrument is provided with 3 full scale sensitivity ranges of 20, 2 and 0.2 mr/hr. corresponding to 60,000, 6,000 and 600 counts per minute. The instrument was calibrated in the factory using gamma rays from a cesium 137 source which is radium equivalent for the Model 15 probe (incorporating the D50 glass wall counter). For checking the calibration of the survey meter, a radium calibration source is provided. The source is contained in a small plastic cylinder mounted at the rear of the instrument case. The background reading of the meter is not appreciably increased if the calibrating source is connected while

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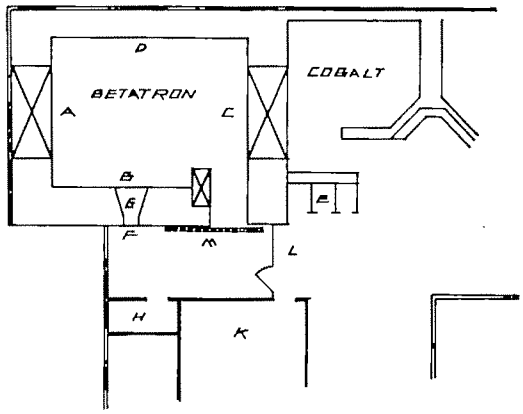


FIG. 2. Floor plan of the installation. (A) Baryte concrete outside wall; (B) concrete inside wall; (C) Baryte concrete wall; (D) concrete outside wall; (E) dressing cabinets; (F) operating panel; (G) window; (H) dark room; (K) biologic laboratory; (L) protective barrier; and (M) sliding lead door.

the instrument is in use. With the calibrating source removed from the vicinity of the instrument, the background reading from cosmic rays will indicate about 1/10 of full scale on the .2 mr/hr. range.

Figures 3 through 8 show the results of the survey for attenuated and scattered radiation from roentgen rays and electrons around and above the betatron room. The dimensions are diagrammatic to bring out the importance of levels at certain structures such as the viewing window, lead door, etc.

NEUTRONS

Roentgen rays and electrons released in megavolt installations above 10 mev. produce neutrons by a process of photodisintegration of certain nuclei. These neutrons are produced by (γ,n) and (e,n) processes in the target, collimators, lead protective blocks within the betatron, etc. In most cases, the initial neutrons will have energies in the range of a few mev. However, they will be slowed down in an absorber forming an energy spectrum extending from the thermal neutrons (less than .02 ev.) to high energy neutrons. The types of interaction between neutrons and surrounding material

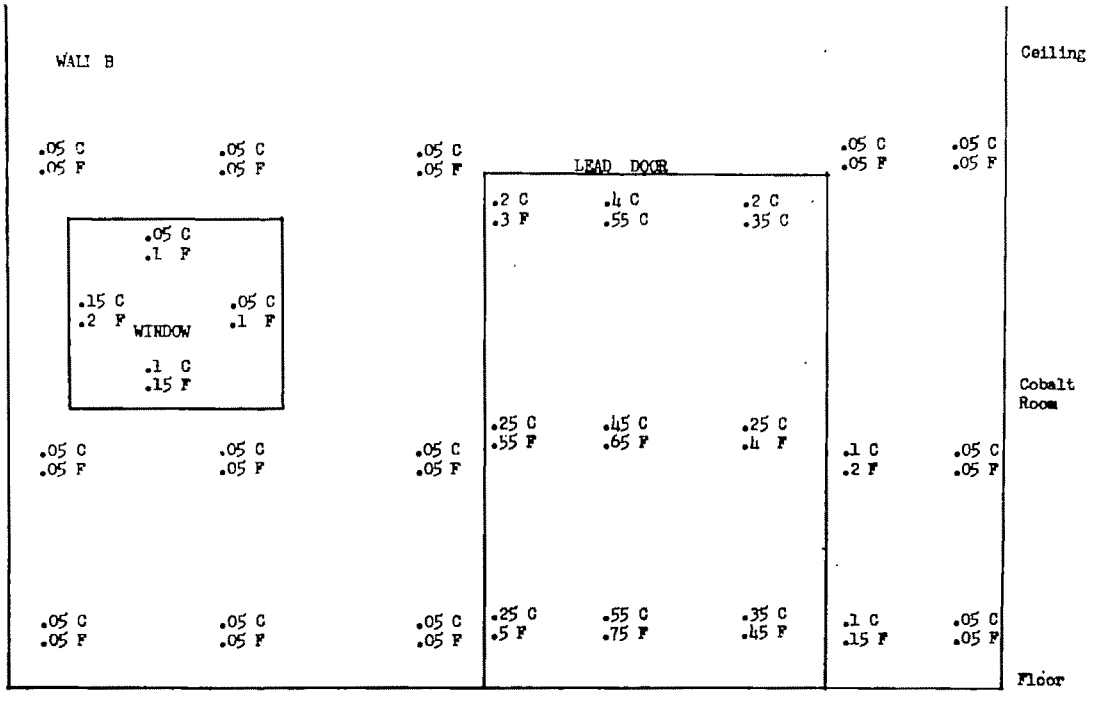


FIG. 3. Scattered radiation measured in mr/hr.: 35 mev. roentgen rays, gamma-4 equalizer; 16×16 cm. field at 100 cm. target skin distance; lucite phantom 30×30×30 cm.; output of the beam 40–45 r/min. C = beam aimed towards cobalt room. F = beam aimed towards floor.

vary considerably with the energy of the neutrons. It is therefore important to classify them according to the energy intervals. Handbook 63, National Bureau of Standards, on protection against neutron radiation up to 30 million electron volts, divides neutrons into the following energy categories:

1. Thermal neutrons, which include all neutrons with energies of less than .5 ev.

2. Intermediate neutrons with energy ranges extending from .5 ev. to 10 kev.

3. Fast neutrons where the range will be considered to extend from 10 kev. to 10 mev.

The slowing down of fast neutrons in an absorber may be treated as a collision problem. Consider a source of initially fast neutrons embedded in a mass of an absorber; the neutrons will lose energy by a series of elastic collisions with the nuclei of the absorber. Neutrons having no electric charge move freely through solid matter and do not lose energy through ionization as do charged particles. Since neutrons do not collide with electrons, but only with nuclei, they travel through many atoms before colliding with a nucleus (*e.g.*, the mean free path of a neutron with a kinetic energy of 2 mev. is about 3.2 cm. in water). As the single neutron makes a series of collisions with the nuclei of the absorber, it transfers its energy to the nuclei as it is scattered within the mass of the absorber. The neutron is usually captured by a nucleus long before it has a chance to decay. Very often, however, before the capture takes place, the neutron loses so much energy that it may reach an average energy of the order of the thermal agitation energy of the nuclei of the absorber. Such neutrons are then called thermal neutrons. Provided the absorber's mass is sufficiently large to prevent the escape of neutrons, it can be shown that the lower the atomic number of the element in which the neutrons are slowed down, the fewer are the collisions required for thermalization; in other words, the greater is the energy loss per collision. Materials which are efficient in slowing down neutrons with-

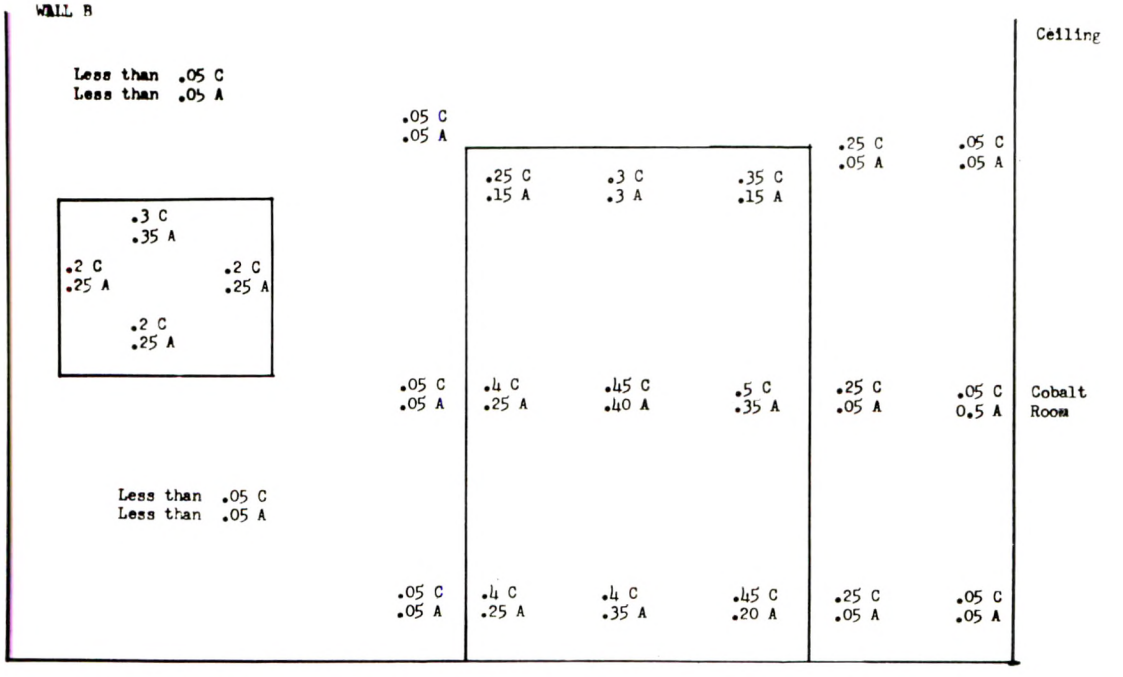


Fig. 4. Scattered radiation measured in mr/hr.: 35 mev. electron beam, beta-1 scatterer; 14×14 cm. cone at 110 cm. target skin distance; lucite phantom 30×30×30 cm.; output of the beam 400–450 r/min. C = beam aimed towards cobalt room. A = beam aimed in opposite direction towards Wall A.

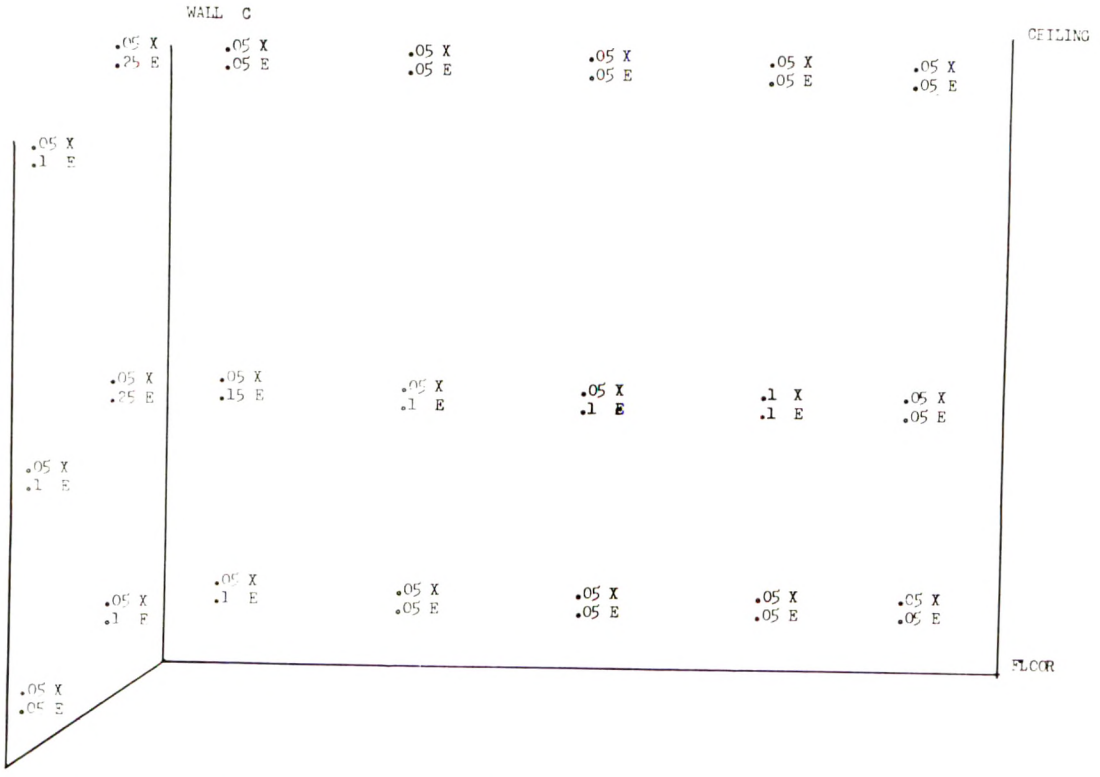


FIG. 5. Scattered radiation measured in mr/hr.: Beam aimed towards cobalt room. X=35 mev. roentgen rays gamma-4 equalizer; 16×16 cm. field at 100 cm. target skin distance. E=35 mev. electron beam, beta-1 scatterer; 14×14 cm. field at 110 cm. target skin distance. Phantom and outputs as in Figures 3 and 4.

out capturing them are known as good moderators.

The most important reaction between fast neutrons and tissue is elastic scattering. In this type of collision the kinetic energy of the neutron and the nucleus remains unchanged and the nucleus is left in the same state as before the collision. The energy absorbed in tissue due to the elastic collision is largely by the absorption of scattered hydrogen atoms. This occurs because the hydrogen atoms are more abundant and because the energy loss of a neutron by collision is inversely proportional to the mass number of the nucleus hit by the neutron in an elastic collision.

$$\text{Average fraction of energy lost} = \frac{2M}{(M+1)^2}$$

where M = mass number of the colliding atom.

For the intermediate and thermal neutrons the dose absorbed in tissue is by neutron absorption according to the H (n,γ) D and N^{14} (n,p) C^{14} reactions. The gamma quantum released in the first reaction has an energy of about 2.2 mev. and the proton from the second reaction has an energy of about 600 kev.

PERMISSIBLE EXPOSURE TO NEUTRONS

Biologic comparisons based on $LD_{50/30}$ appear to indicate that the relative biological effectiveness (RBE) of fast neutrons in acute exposures would be 2–4 (Handbook No. 63, National Bureau of Standards). Continuous low exposure (protraction) and fractionation appear to result in higher RBE for fast neutrons, particularly in injury to tissue not likely to be replenished by cells from other organs (*e.g.*, lens epithelium and germinal epithelium). Calculations show that the RBE depends upon the energy of the neutrons. Table 1 shows RBE

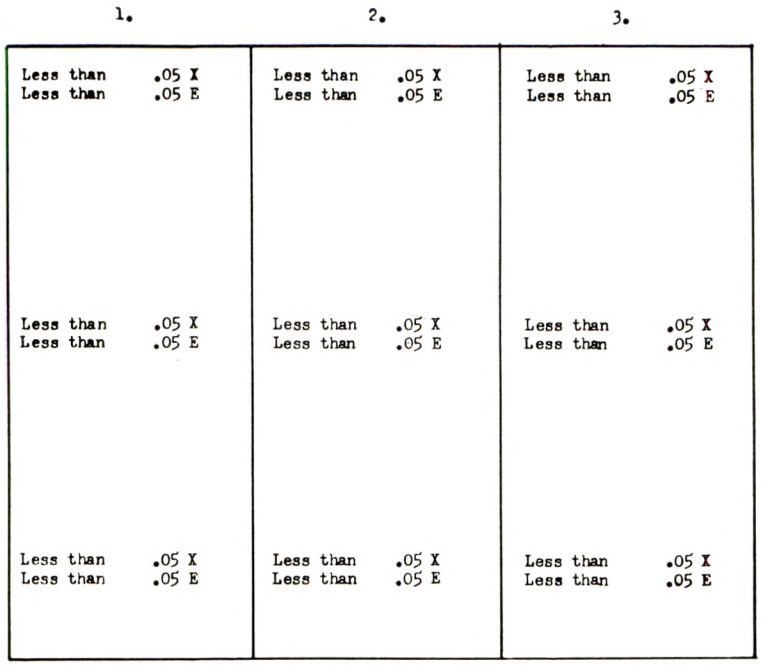


Fig. 6. Scattered radiation measured in mr/hr.: Beam aimed towards cobalt room. X = 35 mev. roentgen rays, gamma-4 equalizer; 16×16 cm. field at 100 cm. target skin distance. E = 35 mev. electron beam, beta-1 scatterer; 14×14 cm. field at 110 cm. target skin distance. Phantom and outputs as in Figures 3 and 4.

and maximum permissible flux of neutrons for protracted exposure on the basis of a 40 hour week. The values in Table 1 apply only to mono-energetic neutrons. Scattering by walls and other structures will cause degradation of neutron energy and the

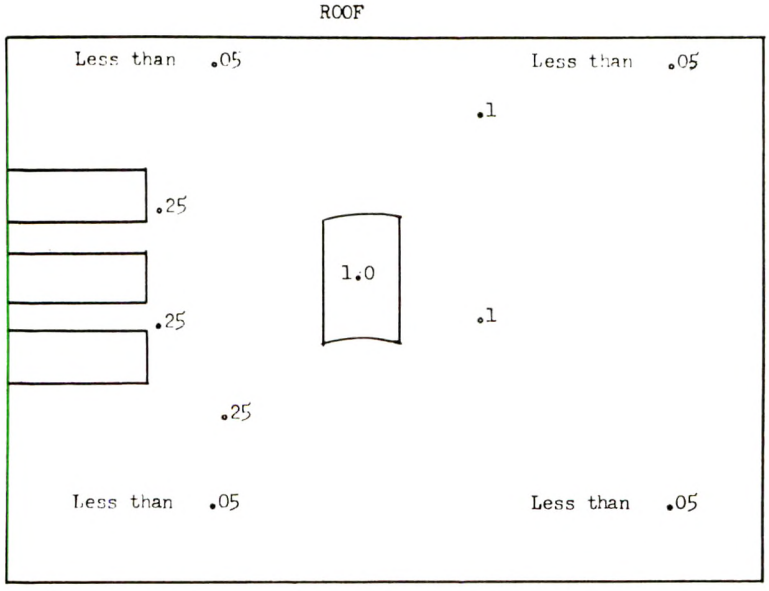


Fig. 7. Scattered radiation measured in mr/hr.: 35 mev. roentgen rays, gamma-4 equalizer; 16×16 cm. field at 100 cm. target skin distance. Phantom and output as in Figure 3. Beam aimed towards cobalt room at the angle of 110 degrees.

TABLE I

MAXIMUM PERMISSIBLE NEUTRON FLUX
Time-average flux for 40 hour week to deliver 100 mrem

Neutron Energy	RBE	100 mrem n cm.$^{-2}$ sec.$^{-1}$
Thermal	3	670
0.0001	2	500
.005	2.5	570
.02	5	280
.1	8	80
.5	10	30
1.0	10.5	18
2.5	8	20
5.0	7	18
7.5	7	17
10	6.5	17
10–30	suggested limit	10

From Handbook 63, National Bureau of Standards.

lowering of the RBE values. However, the spectral distribution of neutron energy is very difficult to measure in our circumstances. For maximum safety reasons we assume that the average energy of neutrons originating from our betatron is 1.0 mev. The RBE associated with neutrons of this energy is 10.

NEUTRON MEASUREMENTS

Measurements were performed using the Model portable 2112 Count-Rate Unit with DN-3 neutron detector of the Nuclear Chicago Company. The instrument is provided with 3 ranges of count-rate indication: 0–150, 0–1,500, 0–15,000 counts per minute. Its sensitivity for fast neutrons is such that approximately 1 count per second is produced in a flux of 10 neutrons per square cm. per second from a radium-beryllium neutron source. The sensitivity for thermal neutrons is such that approximately 3 counts per second are produced in a flux of 10 neutrons per square cm. per second. The calibration of the instrument was checked and verified against standard radium-beryllium neutron sources in the Health Physics Department of the Brookhaven National Laboratories, Upton, Long Island. The instrument provides discrimination against beta and gamma radiation

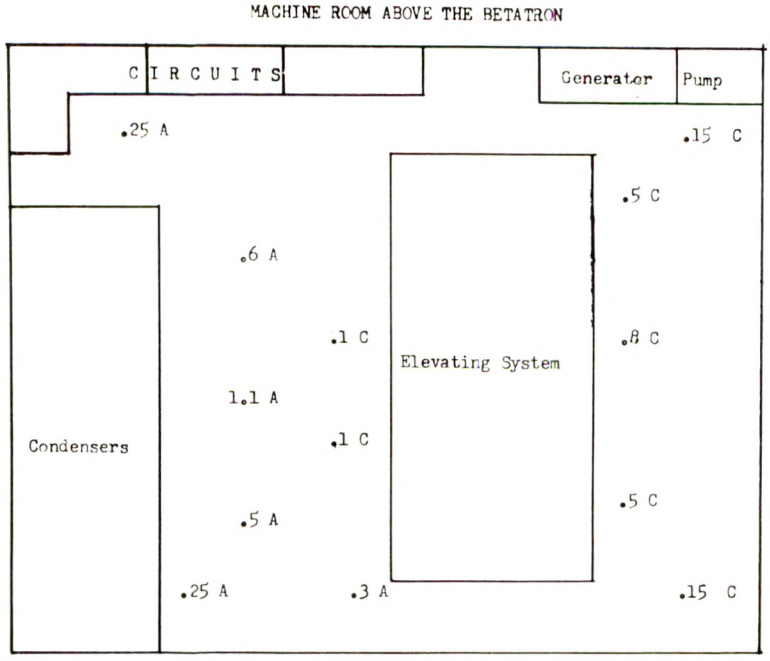


FIG. 8. Scattered radiation measured in mr/hr.: 35 mev. roentgen rays, gamma-4 equalizer; 16×16 cm. field at 100 cm. target skin distance; lucite phantom 30×30×30 cm.; output of the beam 40–45 r/min. C = beam aimed towards cobalt room angled at 110 degrees. A = beam aimed towards Wall A angled at 110 degrees.

by the electrical circuit. The DN-3 detector uses a BF_3 gas-filled chamber for a proportional counting. The boron in the gas is enriched in the B^{10} isotope and the gas is under a pressure of 20 cm. of mercury. The BF_3 gas-filled detector tube is basically a thermal and slow neutron detector. Fast neutrons cannot be detected directly. To count them the cylindrical BF_3 counter is surrounded by about 1 inch of wax (cylindrical) and a 20 mil. cadmium shield around the wax. Fast neutrons striking the wax are slowed down by elastic collisions with the protons in the wax. A definite fraction of all the incident neutrons reaches the BF_3 counter with thermal energy and is counted. The counting rate is therefore proportional to the number of incident fast neutrons. The detector may be used as a thermal and slow neutron energy detector by removing the cadmium shield and wax or by exposing the end of the detector to the neutron flux since the cadmium shield does not cover that section. Neutrons passing through a detector do not produce ionization directly. They can be detected indirectly following their interaction with matter. The reaction used in the DN-3 detector is ${}_5B^{10}+{}_0n^1\rightarrow{}_3Li^7+{}_2He^4$ in which a neutron releases a fast alpha particle from boron nucleus. The released alpha particle leaves a highly ionized track in the gas. These ions are accelerated towards electrodes and produce a pulse which is proportional to the energy of the initial neutron. The pulse from the detector is amplified by a three-stage transistor amplifier with overall voltage gain of about 100. Negative feedback is employed to increase input impedance and to reduce the dependence of the amplifier gain on the transistor characteristics.

DISCUSSION

Measurements taken outside the betatron room show that the radiation level due to the attenuated and scattered roentgen rays and electrons does not exceed 1.0 mr/hr. Actually, the average dose outside the betatron room is of the order of tenths of a mr/hr. This is considerably below the maximum permissible dose of 2 mr/hr. In addition, the corrections for the use and occupancy factor will reduce the dose even further.

Neutron measurements, however, show the penetration of the neutrons scattered from the Wall C throughout the lead door at the entrance to the betatron room. Assuming the average energy of the fast neutrons to be 1.0 mev. and the RBE equal to 10, we derive from Table 1 that the maximum permissible fast neutron flux is 20 neutrons/cm.^{2}/sec. for a 40 hour week to deliver 100 mr. Figures 9, 10 and 11 show the results of the neutron flux measurements around the betatron. Figure 9 shows that the maximum neutron flux in the middle of the lead door is 360 neutrons/cm.^{2}/sec. The average time of betatron operation is presently 8–10 hours per week. However, we assume for purposes of this survey that the operation time of the betatron will reach 12–15 hours per week. This includes patients' treatments, experimental work and physical measurements. Under these assumptions the maximum permissible dose is 50 fast neutrons/cm.^{2}/sec. This would permit the technician or the attending physician to stand at the door for about 2 hours per week during the betatron's operation. Nonoccupational personnel (patients' families, visitors, etc.) could reach a maximum permissible dose of 10 mr per week by standing close to the lead door for a period of slightly over 10 minutes of the machine's operation. The fast neutron flux at the operator's desk was measured to be 10 neutrons/cm.^{2}/sec. Therefore, the technician operating the machine for the total of 15 hours per week would receive $\frac{1}{5}$ of the maximum permissible dose of fast neutrons. However, the machine is used and operated by physicists and researchers in their investigations and the betatron therapy technician spends only a part of the working time of the betatron at the control desk. Naturally, this reduces his weekly exposure.

The maximum permissible slow neutron

Wall B

		LEAD DOOR					
50 F 150 S	200 F 400 S	165 F 250 S	300 F 510 S	265 F 510 S	200 F 300 S	90 F 250 S	15 F 150 S
		300 F 450 S	360 F 800 S	360 F 800 S	280 F 650		
.25 F 150 S	220 F 400 S					110 F 325 S	25 F 200 S
		285 F 800 S	315 F 1050 S	350 F 1150 F	310 F 680		
.25 F 150 S	150 F 500 S	300 F 700 S	300 F 1000 S	265 F 1200 S	265 F 600 S	90 F 450 S	15 F 200 S

FIG. 9. Measurements in neutrons/cm.²/sec.: 35 mev. roentgen rays, gamma-4 equalizer; 16×16 cm. field at 100 cm. target skin distance; mix-D phantom 30×30×30 cm.; output 35–40 r/min. Beam directed towards Wall C. F = fast neutrons. S = slow neutrons.

Wall R

		LEAD DOOR				CEILING	
30 F 150 S	100 F 400 S	150 F 300 S	200 F 500 S	180 F 550 S	165 F 350 S	50 F 250 S	15 F 150 S
		225 F 800 S	260 F 1000 S	260 F 1050 S	220 F 800 S		
30 F 150 S	100 F 450 S	225 F 750 S	270 F 1000 S	270 F 1000 S	250 F 600 S	50 F 250 S	15 F 200 S
30 F 150 S	80 F 450 S	235 F 750 S	250 F 900 S	270 F 950 S	200 F 600 S	80 F 300 S	15 F 200 S

FIG. 10. Measurements in neutrons/cm.²/sec.: 35 mev. roentgen rays, gamma-4 equalizer; 16×16 cm. field at 100 cm. target skin distance; mix-D phantom 30×30×30 cm.; output 35–40 r/min. Beam directed towards the floor. F = fast neutrons. S = slow neutrons.

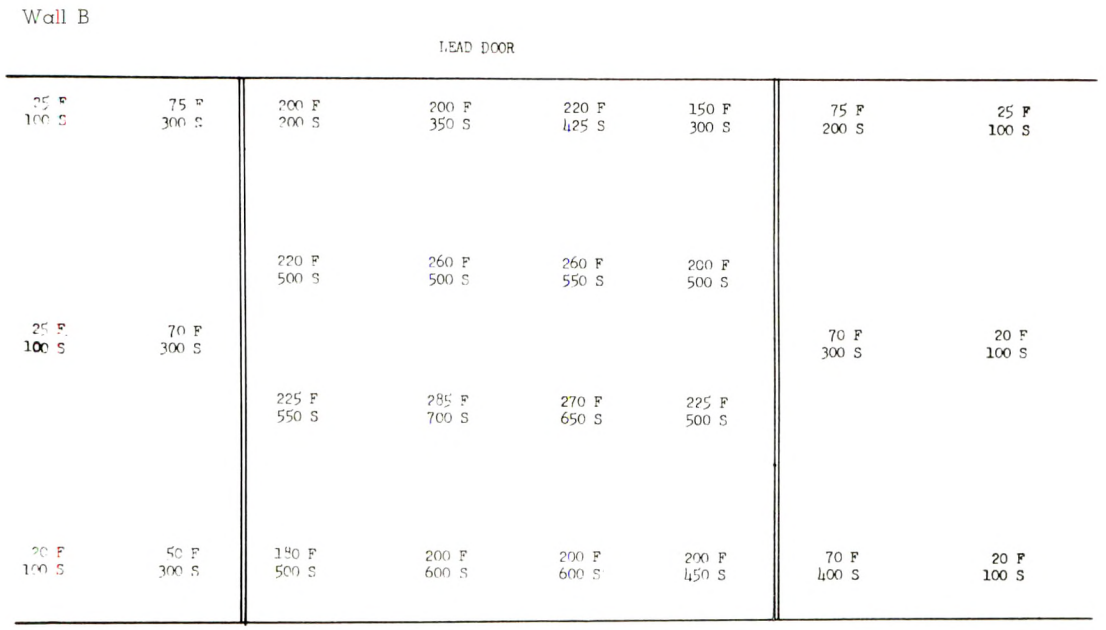


FIG. 11. Measurements in neutrons/cm.^{2}/sec.: 35 mev. electron beam, beta-1 scatterer; 14×14 cm. field at 110 cm. target skin distance; output approximately 500 r/min. Beam directed towards Wall C. F = fast neutrons. S = slow neutrons.

flux for 40 hours per week to deliver 100 mr is about 15 times that of the fast neutron level (see Table 1). It is evident from the measurements on Figures 9, 10 and 11 that slow neutron levels are far below the maximum permissible dose (letter S indicates slow and thermal neutrons).

In order to reduce to a minimum the radiation hazard from neutron exposure to the operating staff as well as to the nonoccupational personnel, a barrier built across the corridor (Fig. 2.L) restricts access to the area adjacent to the betatron room. If the barrier is opened while the betatron is in operation, an electrical interlock will stop radiation immediately. Accepted radiation labels are posted in the restricted area. In addition, each member of the professional staff connected with the betatron work is monitored for fast neutrons by means of neutron film badges.

SUMMARY

A radiation protection survey was performed around a 35 mev. betatron unit. Radiation levels caused by 35 mev. roentgen rays and 35 mev. fast electrons were checked in all rooms adjacent to the betatron room. Tabulated results show that the concrete and baryte concrete walls provide excellent protection for roentgen-ray and electron radiation. Neutrons originating in the lead collimators through (γ,n) photonuclear reaction and passing through the lead door were counted. Fast and slow neutron fluxes are tabulated in Figures 9, 10 and 11. Results are discussed and ways are presented to ensure minimum exposure to operating personnel and nonoccupational individuals.

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THE IMPORTANCE TO RADIOLOGISTS OF RECENT ADVANCES IN CYTOLOGY AND CYTOGENETICS*

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BEFORE the turn of the present century, several pathologists had observed and described large, bizarre cells in the blood of patients with advanced cancer, which were interpreted as probably being tumor cells. However, despite extensive investigations by pathologists of the invasion of blood vessels and lymphatics with cancer, it was not until 1934 that two young Boston surgeons made the first systematic search for tumor cells in the blood.[14] This study attracted little attention and more than 20 years elapsed before their findings were confirmed.

A resurgence of interest in this field followed Engell's[3] report in 1955 in which he described the frequency of cancer cells in the peripheral blood and from blood obtained during surgery from regional veins draining the tumor site of cancer patients. Engell prepared concentrated masses of the buffy coat from 5–10 ml. of blood by hemolyzing the red blood cells and centrifuging down the remaining cellular elements. Over 50 per cent of the blood samples from veins draining colon carcinomas contained tumor cells.

In the last 7 years there have been nearly 100 similar reports by various investigators throughout the world. The techniques for the isolation of tumor cells in the blood used by different groups have varied greatly. As yet, no completely satisfactory method for isolating and concentrating tumor cells from the blood has been discovered. The methods utilized have included sedimentation or hemolysis of erythrocytes with subsequent concentration or fractional flotation of the tumor cells; or isolation by filtration of the cellular elements following destruction of the red blood cells. One of the major shortcomings of the studies of tumor cells in the blood has been a lack of uniform standards for the definition of tumor cells and, more importantly, sufficient trained personnel capable of identifying such cells in the blood. Since many abnormal cells, which can be confused with tumor cells, are present in the blood of cancer patients, the morphologic criteria for the identification of these cells and considerable experience in the study of the morphology of such cells become paramount factors in the reporting of the incidence of cancer cells in the blood.

In Table 1 are shown the average frequencies of occurrence of tumor cells in the peripheral and regional blood as reported by various authors. The results presented should be interpreted with caution. For example, the frequency with which tumor cells are detected in the blood is increased if patients with advanced malignancy are studied and if serial samples are examined. Indeed, if 2–4 serial samples of 25–50 ml. of blood are examined, it is possible that circulating tumor cells could be found in the blood of most patients with advanced can-

TABLE I

FREQUENCY OF TUMOR CELLS IN THE REGIONAL AND PERIPHERAL BLOOD OF PATIENTS WITH VARIOUS CANCERS

Organ Site	Per Cent Regional Blood	Per Cent Peripheral Blood
Breast	50	20
Lung	80	50
Stomach	50	20
Colon-Rectum	30	5

* From the Roswell Park Memorial Institute, New York State Department of Health, and the Medical Foundation of Buffalo, Buffalo, New York.

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cer. The relative frequency of circulating cancer cells varies greatly with different kinds of cancer and usually correlates closely with the frequency of blood vessel invasion observed in histologic sections of the tumor. For example, vascular invasion is seen in 80 per cent of histologic sections from lung cancers. This is approximately the same frequency with which one finds tumor cells in the regional venous blood. This is also true for breast cancer where the figure is about 50 per cent and for colon cancer where it is just below 30 per cent. These figures are only approximations, and, of course, they will vary with the stage of the disease and the thoroughness of the studies.

The most intriguing aspect of these studies is the remarkable infrequency with which these blood-borne tumor cells survive and establish themselves as metastases. While no precise computations are possible, if one compares the frequency with which tumor cells are found in the blood with the frequency of blood-borne metastases, it appears that over 99 per cent of the exfoliated tumor cells do not survive. We have successfully cultivated tumor cells from the blood in tissue cultures so that there can be little doubt regarding the viability of such cells.[11] This has been widely confirmed with studies of tumor cells from the blood of experimental animals. These findings offer substantial evidence that the cancer patient is capable of controlling or destroying some of his own tumor cells. This is a field of investigation that needs extensive study.

There are potential studies in which the collaboration of radiologists would be most welcome. We need to learn, among other things, more about the influence of radiation on (1) tumor cell spread; (2) the viability of exfoliated cells; (3) alteration of the tumor vascular beds; and (4) alterations of the biologic characteristics of both tumor and normal cells.

In order to effectively pursue such studies, radiologists, internists, and surgeons and, indeed, all clinicians must become

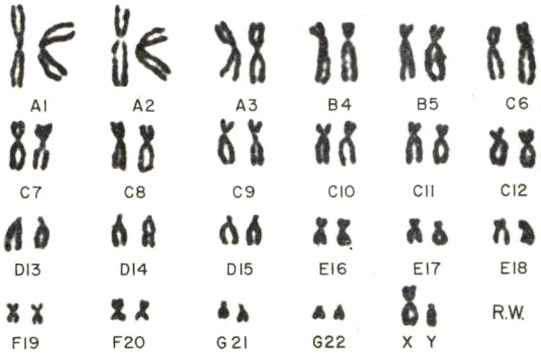


Fig. 1. Karyotype of bone marrow cells of normal human male. Twenty-two pairs of autosomes are shown and one pair of sex chromosomes (X and Y). In the female two X chromosomes are present and the Y is absent.

better acquainted with cytogenetics. Progress in this area during the past few years has been phenomenal and only a few highlights can be given here. For many years, we were taught that human cells had 48 chromosomes. However, the careful and critical studies of Tjio and Levan[21] and of Ford and Hamerton[5] (reported in 1956) showed that the correct number for the human is 46 (Fig. 1). Shortly thereafter, the presence of additional sex chromosomes or a loss of a sex chromosome in patients with developmental abnormalities was described.[15] In 1959, Lejeune and co-workers[9] showed that mongolism was associated with a chromosomal abnormality characterized by the presence of an extra, small autosome, or "chromosome 21 trisomy" (Fig. 2). Since that time a host of scientists have joined in the search for other cytogenetic clues to disease. There are several recent reports which would be of invaluable aid in initial educational efforts in this field. "Chromosomes for Beginners,"[10] "Chromosomal Aberrations in Human Disease,"[7] and "Recent Progress in Human Chromosome Analysis and Its Relation to the Sex-Chromatin"[19] are particularly recommended.

The existence of wide variations in the chromosome numbers of various tumor cells has been known for many years.[6] Frequently, the "excess" amount of chromo-



Fig. 2. Metaphase from a cultured blood cell of a female child with mongolism. Arrows point to the 5 G-group chromosomes. In a normal subject, only 4 of these chromosomes are present and in the preponderant number of cases with mongolism, an extra chromosome in this group characterizes the disease. (Photograph kindly supplied by Dr. T. S. Hauschka.)

some material was so vast that it could be detected by histochemical and spectrophotometric methods. In other cases, however, the total amount of DNA in cancer cells was normal. With the introduction of new techniques for culturing cells and preparing chromosomes for morphologic study, it became apparent that cancer cells might have the proper number of chromosomes but that some of the chromosomes were often abnormal morphologically (Fig. 3).

An important contribution to human leukemia was the description by Nowell and Hungerford[12] of an abnormally small chromosome (Ph[1]) in the cells of patients with chronic myelocytic leukemia. We have observed this anomalous autosome (G-22) in 14 of our 19 patients with chronic myelocytic leukemia. The cells of 5 patients with somewhat atypical chronic myelocytic leukemia, including 2 patients with probable radiation-induced leukemia, did not have the Ph[1] chromosome and may represent another kind of myelocytic leukemia.[18] Whether this chromosome abnormality (Ph[1]) is directly associated with the cause of one particular kind of chronic myelocytic leukemia remains to be determined. No specific or uniform changes have been found in the chromosome constitution of cells in acute leukemia.[17]

A much broader spectrum of abnormal chromosome constitution, both in numbers and morphology, has been found in the karyotypes of tumor cells in malignant effusions.[8] Chromosome numbers of such human cancer cells have ranged from less than 40 to several hundred. Some of these cells have unusual chromosomes. These may involve such aberrations as excessive length, bizarre forms, minute and fragmented forms, ring structures, etc.

Radiologists should be particularly interested in such chromosomal alterations since many of these abnormalities may be induced by radiation. A large body of evidence has accumulated in the literature regarding the biologic effect of various forms of radiation. The higher incidence of various forms of leukemia, including chronic myelocytic leukemia, following ionizing radiation has been well documented in

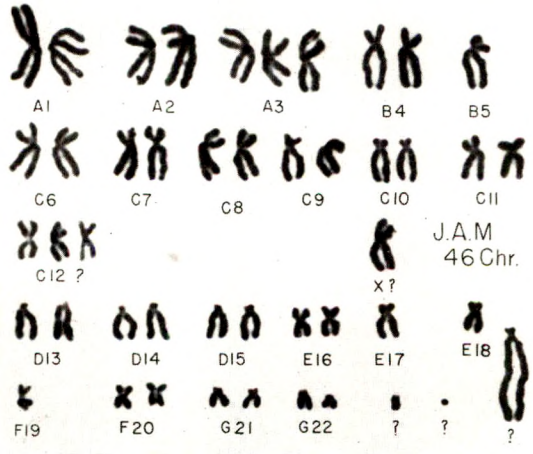


Fig. 3. Karyotype of a cancer cell from an effusion of a male patient with cancer of the colon. Note that although 46 chromosomes are present, there are at least 3 abnormal chromosomes (lower right corner) and missing or extra chromosomes in the other groups. In particular, compare this karyotype with that of the normal male shown in Figure 1.

Japan, England and the United States. At our Institute we have observed a case of chronic myelocytic leukemia following I^{131} therapy for metastatic carcinoma of the thyroid.[13] A number of cases of acute leukemia has been described following such therapy. Of utmost importance is the recent observation that small doses of ionizing radiation may produce definite chromosomal changes in human subjects. Tough *et al.*[22] in England reported that vertebral radiation therapy for rheumatoid spondylitis produced an abundance of chromosomal abnormalities in leukocytes cultured from the blood. Chromosomal aberrations following therapeutic doses of I^{131} have also been reported by us[16] and by Boyd *et al.*[2] from England.

Recently, Bender and Gooch[1] described abnormal karyotypes in short-term cultures of leukocytes from the peripheral blood of men exposed 29 months previously to mixed gamma rays and fission neutron irradiation. Abnormal chromosome numbers ranged from 7 to 23 per cent in 5 men who were exposed to irradiation estimated to be over 230 rads. Aberrant chromosome forms were also described.

More disturbing is the report by Stewart and Sanderson[20] that chromosomal abnormalities were observed after diagnostic roentgen irradiation, but this study awaits confirmation in other laboratories. We have examined the chromosomal changes in the marrow cells of patients with hyperthyroidism before and after I^{131} therapy (5–15 mc). Alterations in chromosome numbers and morphology in bone marrow cells were noted following radioisotope administration (Tables II and III and Fig. 4). Four weeks after therapy the chromosomal changes had disappeared. It should be pointed out, however, that recent evidence indicates that the resurgence of abnormal mitotic activity may occur in the marrow, 4 to 6 months after exposure to ionizing radiation.[4] Such findings point to the need for long-term, follow-up chromosome studies in such patients.

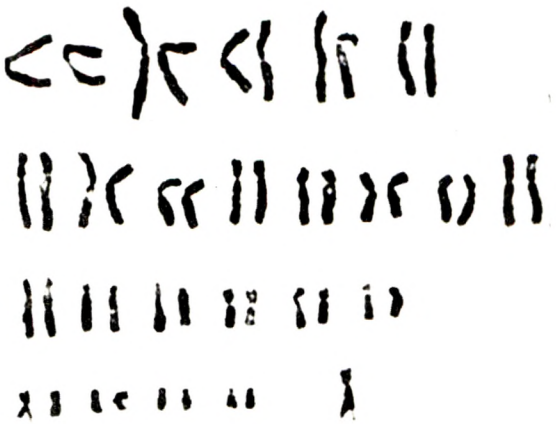


Fig. 4. Karyotype with 47 chromosomes of a bone marrow cell from a female patient D. W. 3 days after receiving I^{131}. A substantial number of these cells had 47 chromosomes (See Table III). The extra chromosome is shown at the end of the karyotype and consists of a medium-size metacentric unit.

Table II

Chromosome constitution of marrow from 23 patients treated with I^{131}

	Chromosome Number		Total Cells Counted	Per Cent Aneuploid Cells
	46	>< 46		
Before therapy	708	68	786	9
3–5 days after therapy	284	142	426	33
4–6 weeks after therapy	681	32	713	5
Nonthyroid controls	1,448	201	1,649	12

Concluding Remarks

The era of cytogenetics is just beginning. Improved techniques of culturing human cell and technical advances in the preparation of materials for chromosome study should permit many new observations of interest to radiologists. Perhaps the electron microscope and other instruments with a higher power of resolution can be used to extend and make more precise our classification of abnormal chromosomes. The limitations of purely morphologic studies will become increasingly apparent; however, fu-

TABLE III

CHROMOSOME CHANGES IN PATIENT D.W. AFTER 5 MC OF I^{131}

	Chromosome Number										
	42	43	44	45	46	47	48	49	50	51	52
Control			1	4	56	4					
3 days after therapy	1	1	3	6	28	10	3	1	1	1	1
4 weeks after therapy				2	36	4					

ture physicochemical and biologic studies of the abnormal nucleic acids will need to be correlated with the morphologic studies. The enormity of the problem is evident when one considers that a chromosome may contain 40,000 or more gene-sites.

It is to be hoped that it might be possible to produce specific chromosome defects with irradiation or by other means, and identify associated specific metabolic or genetic alterations. Perhaps it will be possible to culture pure clones of such cells, and then grow 100–1,000 grams of these cells in spinner cultures, much like the successful growth of many kilograms of a particular bacterium. The next step would be the isolation of individual chromosomes and the chemical identification of the abnormal genetic materials.

Radiologists are in a unique position as regards this research. They have the opportunity to observe, control and initiate cytogenetic abnormalities in the clinic and in the laboratory. The future possibilities of such studies are unlimited.

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EFFECTS OF THE PROLONGED INTRAVENOUS AND INTRA-ARTERIAL INFUSION OF CANCER CHEMOTHERAPEUTIC COMPOUNDS*

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DESPITE the current enormous undertaking of cancer research to provide anticancer drugs for use in the management of neoplastic disease in man, no chemical agents have been developed that when given systemically are capable of inducing a general curative effect on disseminated forms of cancer.

In the clinical evaluation of most cancer chemotherapeutic agents, the drugs are usually given by single daily administration. It appeared important to explore other dose schedules to determine all possible biologic effects of these compounds. A major part of our clinical cancer chemotherapy program is concerned with studies of the effects of varying the duration and route of administration of these compounds.

In this report a series of clinical studies is described in which several antimetabolites and antibiotics were given by continuous 24 hour intravenous and intra-arterial infusion until maximal local and systemic effects were obtained.

PROLONGED INTRAVENOUS INFUSION CHEMOTHERAPY

FLUORINATED PYRIMIDINES

We have reported that the biologic effects of several fluorinated pyrimidines are clearly altered by prolonged infusion.[13] The toxicity of 5-fluorouracil (FU) was diminished so that the compound was tolerated at a dose of 15 mg. per kg. per 24 hours for as long as 37 days. This would represent a supralethal dose if the agent were given by single daily administration. In contrast, the known toxicity of 5-fluoro-2′-deoxyuridine (FUDR) was greatly enhanced, with maximal tolerated toxicity developing at doses as low as 0.5 to 1.0 mg. per kg. per 24 hours for 7 days (1/30 to 1/60 the usual single daily dose).

Our studies of the clinical effects of the 24 hour infusion of FUDR suggest that the metabolic fate of the compound is altered[4] and that the therapeutic index may be increased.[11] Of 67 patients with advanced cancer who were evaluated for therapeutic effect, objective tumor regression was noted in 29 (Table 1). It is our impression that continuous intravenous infusion of FUDR is a more feasible method of its administration, since it is apparently acting to interfere with thymidine synthesis.[4,8] FUDR has been shown to be most active biologically when its antimetabolic effect interferes with thymidine synthesis.

MISCELLANEOUS COMPOUNDS

We have reported that the biologic effects of certain other antimetabolites and antibiotics are altered by prolonged infusion.[4] The toxicity and therapeutic effect of methotrexate (Mtx) is increased by continuous intravenous infusion, while the effects of mitomycin-C and streptonigrin are diminished. The maximum tolerated dose of these compounds by continuous infusion is: Mtx—5 mg. per 24 hours for 4 to 7 days; mitomycin-C—300 gamma per kg. per 24 hours for 6 to 7 days, and streptonigrin—10 gamma per kg. per 24 hours for a period of 6 to 7 days. The therapeutic effects of these compounds were quantita-

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tively and qualitatively similar to those observed with the usual method of administration (single daily injection). Varying degrees of toxicity were noted whenever therapeutic effect was obtained. Somewhat less toxicity for equivalent therapeutic effect was found with mitomycin-C and streptonigrin when given by prolonged administration.

These studies have shown that the prolonged intravenous administration of several cancer chemotherapeutic compounds (antimetabolites and antibiotics) may alter quantitatively the toxic and therapeutic effects as well as modify the metabolic fate of these compounds in the human.

Table I

RESULTS OF PROLONGED INTRAVENOUS INFUSION OF FUDR

Site of Disease	Patients Evaluated (no.)	Objective Tumor Regression (no.)
Lung	8	4
Breast	13	6
Colon and rectum	13	7
Stomach	8	3
Mycosis fungoides	3	3
Miscellaneous carcinoma and sarcoma	22	6
Total	67	29

PROLONGED ARTERIAL INFUSION CHEMOTHERAPY

Prolonged arterial infusion chemotherapy has been developed in an effort to enhance the antitumor effects of compounds on patients who have advanced, but locally confined, cancer. Many forms of malignant neoplasms remain localized throughout their clinical evolution and produce disability and death as a result of their relatively localized yet uncontrolled growth. This is particularly true of most forms of head and neck cancer, primary brain tumors, cancer of the cervix, and often, cancer of the bladder. Moreover, many patients with cancer of the large bowel have increasing disability because of liver metastases, although the primary lesion has been controlled. These forms of cancer often can be controlled by regional cancer chemotherapy.

We have previously reported the rationale for continuous arterial infusion therapy, techniques of catheter introduction in various sites and infusion assembly, complications of therapy and our preliminary results using Mtx, FU and FUDR.[6,7,9–12] Briefly, this method of therapy embodies the 24 hour infusion of cancer chemotherapeutic agents through polyethylene catheters inserted into the arterial blood supply of tumors. The compounds are infused continuously for periods of 7 to 30 days or more, alone in doses which the entire body can tolerate, or in supralethal doses, and the specific antidote is administered systemically by a different route to protect vulnerable areas of the body.

This method of therapy is to be distinguished from extracorporeal isolated perfusion as described by Creech *et al.*[2] The latter technique involves the temporary exclusion of the tumor-bearing area from the general circulation for periods of 30 to 60 minutes, during which time high concentrations of a drug are perfused in the isolated part. In general, the best results from perfusion have been obtained with the rapidly acting alkylating agents, while with arterial *infusion* the most striking effects have been observed with the slower acting antimetabolites—compounds having more finite loci of antimetabolic activity.

PATIENT SELECTION

Patients with advanced uncontrolled yet localized forms of cancer are suitable candidates for therapy. These include: patients with various types of untreated or recurrent primary cancer of the head and neck whose disease is confined to the distribution of the carotid arterial systems; patients with advanced cancer of the cervix or bladder in whom the symptomatic disease is contained within the area supplied by both hypogastric arteries; pa-

tients with primary or secondary brain tumors who may be treated by arterial infusion chemotherapy through catheters inserted into one or both carotid arteries or one vertebral artery; patients with primary or secondary tumors in the liver may be treated through catheters placed directly into the hepatic artery; and patients with neoplasms of an extremity or the chest wall or other sites, in whom the arterial blood supply is accessible, can be treated through catheters inserted directly or retrograde into the desired vessel.

CATHETER INSERTION

Several methods of catheter introduction have been studied and many have been abandoned owing to inherent problems relating to catheter localization and fixation. Accessible arteries of extremities, the aorta, the common or internal carotids and the brachial arteries can often be catheterized by a percutaneous technique. The method most commonly employed at the Lahey Clinic for catheterization of the hepatic artery, celiac axis and hypogastric arteries is by direct (operative) catheter introduction. After adequate exposure and control of the artery to be catheterized, a length of polyethylene tubing swaged onto a round-bodied needle is introduced into the artery by inserting the needle into the lumen and bringing it out of the vessel at the exact, desired site of the location of the tip of the catheter. Subsequent displacement of the catheter is obviated by the placement of a No. 000 silk suture at the point of entrance of the catheter into the vessel.

The carotid arterial system may be conveniently and simply catheterized by the introduction of the tubes into one or both superficial temporal arteries and passed retrograde to the desired site within these vessels.

The fate of the catheter following infusion therapy is predicated upon the vessel catheterized. Catheters inserted into the carotid arterial systems and other accessible peripheral arteries are removed by manual traction. Those inserted into the hepatic and hypogastric arteries are disposed of by placing 5 cm. or more into the subcutaneous tissue at the site of emergence of the catheter on the skin.

DETERMINATION OF AREA OF INFUSATE

An accurate knowledge of the exact area to be infused through the arterial catheter is mandatory. If the tumor is confined to the area of infusion, its entirety will be subjected to the biologic effects of the antitumor agent. On the other hand, if only a part of the tumor is within the distribution of the artery infused, the disease outside the area of infusion will not be affected by the arterial infusate. Several methods are employed to demonstrate the area of infusion. These include angiography, fluorescein dye illumination and the distribution of radioactive isotopes.

The simplest and most accurate method of delineating the capillary bed of arteries supplying superficial areas such as skin and mucosa or certain viscera (visualized at operation) can be determined by injection of a fluorescent dye. This technique is utilized at the time of placement of a catheter at any site or whenever there is reason to suspect displacement of the catheter. A total of 3 to 6 cc. of 5 per cent fluorescein is injected into the catheter. Ultraviolet illumination will superficially delineate the area of infusion. Fluorescence persists for 15 minutes or more. In the internal carotid artery a variable amount of fluorescence will be seen on the side injected, including the eye, palpebrae and the forehead areas (Fig. 1).

INFUSION ASSEMBLY

The infusion assembly is put in operation directly after catheter placement and glucose and water or saline solution is infused to maintain patency of the catheter until specific chemotherapy is initiated. A No. 20 gauge needle is inserted into the free end of the polyethylene catheter and connected to rubber tubing which is passed through the fingers of an infusion pump* and thence to liter bottles of infusate (Fig. 2, *a* and *b*).

* Bowman infusion pump, manufactured by Process and Instruments Co., New York, New York.

DRUG DOSE SCHEDULES

An adequate course is defined as that amount of therapy that results in moderate local toxicity within the area of infusion (erythema of the skin, mucosal ulcerations) with or without the development of moderate systemic toxicity. After an adequate course of therapy has been given (usually 10 to 30 days of continuous infusion), the patient is rested until all toxicity has abated, then additional courses are given until maximum clinical response has occurred. In most cases, optimal clinical response has been observed by the end of the second or third course of therapy.

(*a*) *Arterial Methotrexate* (*Mtx*) *Infusion Therapy Combined with Intramuscular Citrovorum Factor* (*CF*). The usual schedule employed for unilateral catheterization is Mtx, 50 mg. per 24 hours, and for bilateral catheterization, 25 mg. per side per 24 hours. CF is given intramuscularly in the dose of 6 mg. every 6 hours. The dose of Mtx is infused in 1,000 cc. to 1,500 cc. of glucose in water per side per 24 hours.

(*b*) *Arterial Mtx Infusion Therapy*. Mtx without the concomitant use of CF is given in the dose of 3 to 10 mg. per 24 hours for unilateral therapy and 2 to 4 mg. per 24 hours for bilateral therapy.

(*c*) *Fluorinated Pyrimidine Infusion Therapy*. These compounds are administered by arterial infusion in the following dose schedules: FU—7.5 to 15.0 mg. per kg. per 24 hours; FUDR—0.1 to 0.3 mg. per kg. per 24 hours.



Fig. 1. Ultraviolet illumination of the distribution of fluorescein injected into the left internal carotid artery.

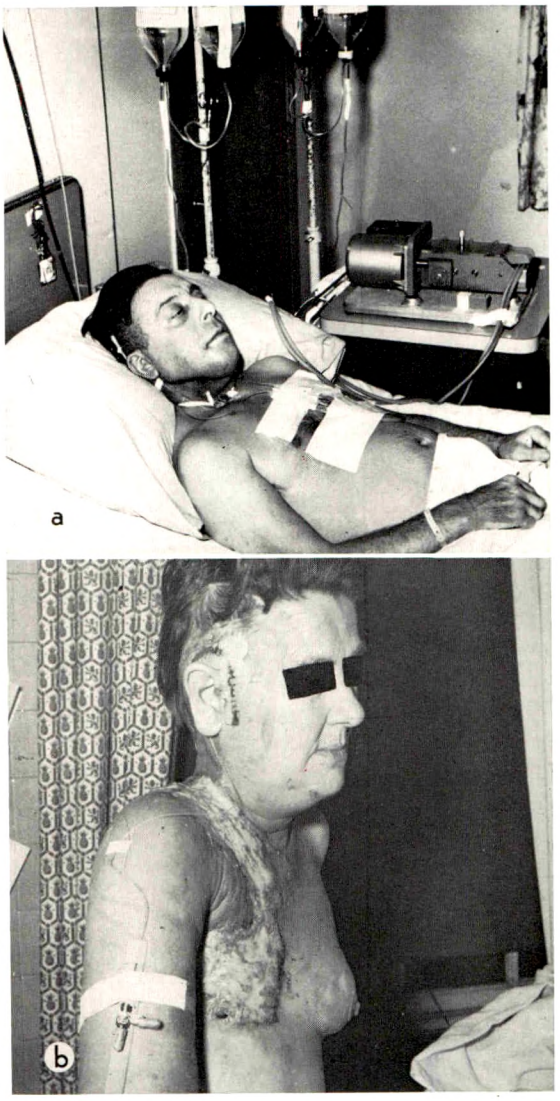


Fig. 2. Retrograde catheter insertion through the superficial temporal artery and infusion assembly. (*a*) Infusion of both common carotid arteries in a patient with cancer of the hypopharynx. (*b*) Infusion of the right innominate artery in a patient with recurrent cancer of the right breast.

RESULTS OF CONTINUOUS ARTERIAL INFUSION THERAPY

Evaluation of clinical results to date is limited to studies using arterial Mtx and intramuscular CF,[1,3,6,8,15,16] Mtx alone,[5]

and to a lesser extent, the fluorinated pyrimidines.[11,14] In general, when the disease has been limited to the area of infusion, results have been good in terms of objective tumor regression and clinical benefit. When contiguous disease was present outside the actual area of infusion, although definite evidence of objective tumor regression has been seen in the treated areas, the disease outside the treated area was unaffected by therapy and little clinical benefit was noted by the patient.

Several cases are presented to illustrate drug dose schedules, local antimetabolic effects and antitumor effects that have resulted from therapy.

ILLUSTRATIVE CASES

Case 1. *Epidermoid Carcinoma of the Cervix.* The patient was a 35 year old Negro woman in whom a diagnosis of epidermoid cancer of the cervix was made by biopsy in January, 1960. The cervix was replaced by a fungating mass and the tumor extended to the vaginal walls (Fig. 3*a*). The uterus was fixed by masses extending to the pelvic walls. Bilateral hypogastric artery catheters were inserted and the patient received arterial Mtx in the dose of 25 mg. per side per 24 hours and intramuscular CF in the dose of 6 mg. every 6 hours. Over a 25 day period, the patient was given 12 days of therapy. There was progressive decrease in visible tumor and by the 29th day after treatment was begun, there was no clinical evidence of residual cancer (Fig. 3*b*). The patient has remained clinically well and has experienced normal menstrual periods for 25 months to date.

Case 11. *Epidermoid Carcinoma of the Bladder.* The patient was a 56 year old white man in whom the diagnosis of inoperable epidermoid carcinoma of the bladder was made in October, 1960. For several months prior to arterial infusion therapy, he had noted constant dysuria and hematuria. An intravenous pyelogram showed nonvisualization of the left kidney and a small bladder with a filling defect on the left side (Fig. 4*a*). An 11 day course of Mtx, infused

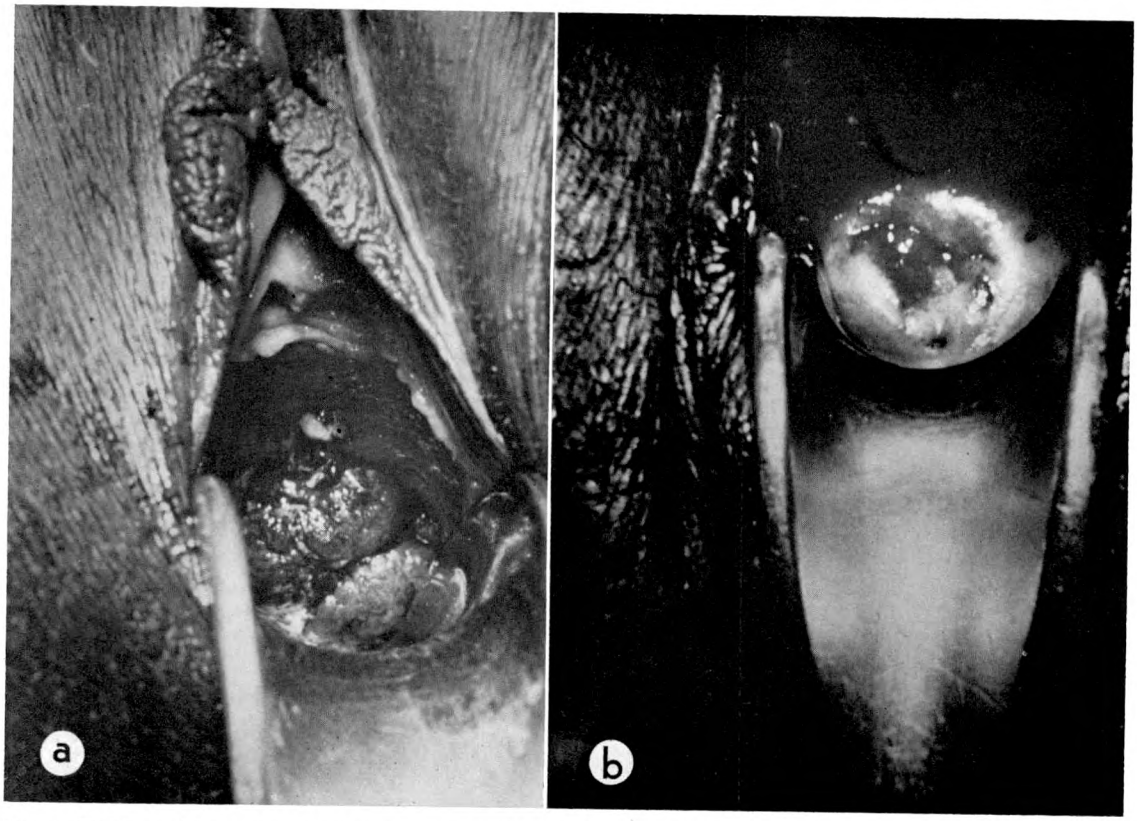


Fig. 3. Epidermoid carcinoma of the cervix. (*a*) Before therapy. Note the extensive fungating lesion extending to the vaginal wall. (*b*) After therapy. Complete apparent tumor regression has occurred

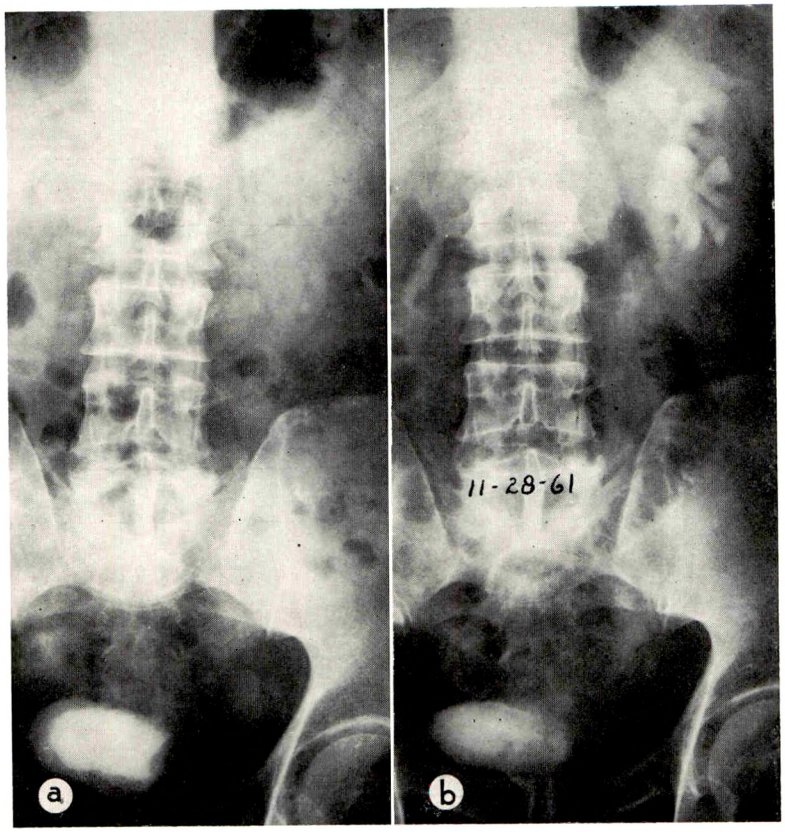


Fig. 4. Epidermoid carcinoma of the bladder. (*a*) Before therapy. Intravenous pyelogram showing nonfunction of the left kidney and a filling defect of the left side of the bladder. (*b*) After therapy. Note the improved function of the left kidney and the decrease in size of the filling defect of the bladder.

into both hypogastric arteries in the same dose as that used for Case I, was given. Hematuria ceased by the 6th day of therapy and the patient became asymptomatic. Cystoscopy following treatment showed that the bladder tumor had regressed by approximately 90 per cent and several urethral lesions had completely disappeared. An intravenous pyelogram showed good concentration of the contrast material on the left side with a moderate degree of hydronephrosis (Fig. 4 *b*). In addition, there was improvement in the filling defect on the left side of the bladder. The patient was asymptomatic for 3 months when hematuria recurred. Further therapy was refused.

Case III. *Adenocarcinoma of the Bowel—Effects of Arterial FUDR Therapy*. The patient was a 56 year old white woman with recurrent cancer of the sigmoid colon, involving the pelvis and vagina. She received a 7 day course of FUDR therapy in the dose of 0.13 mg. per kg. per side per 24 hours through bilateral hypogastric artery catheters. A moderately severe erythema with focal areas of superficial ulceration was noted over the distribution of the terminal branches of the hypogastric arteries (Fig. 5). There was partial decrease of the pelvic and vaginal tumor. Despite maximal local antimetabolic effects, there were no manifestations of systemic toxicity.

DISCUSSION

The over-all results of our experiences with prolonged arterial infusion therapy are tabulated in Table II. Although 91 patients were catheterized, 70 patients received an adequate course of therapy as described above, and 65 were evaluated for therapeutic effect. Forty patients showed partial regression of tumor. Most of these patients had tumor in contiguous areas outside the area of infusion. Little clinical benefit was appreciated by the

Table II

RESULTS OF PROLONGED ARTERIAL INFUSION THERAPY

	Catheterization	Adequate Course of Therapy	Evaluation for Therapeutic Effects	Tumor Response	
				Partial	Total
Head and Neck Cancer					
External carotid artery	59	49	45	25	14
Brain Neoplasms					
Internal carotid artery	14	8	8	6	0
Pelvic Cancer					
Hypogastric arteries	13	10	10	7	1
Liver Tumors					
Hepatic arteries	5	3	2	2	0
Total	91	70	65	40	15

patients because of progression of growth in these latter areas. Fifteen patients whose disease was limited to the area of infusion obtained complete, sustained tumor regression associated with clinical benefit. This latter group consists of patients with epidermoid carcinoma and soft tissue sarcoma of the head and neck region and epidermoid carcinoma of the cervix. Complete, sustained tumor regression has persisted for periods of over 25 months to date.

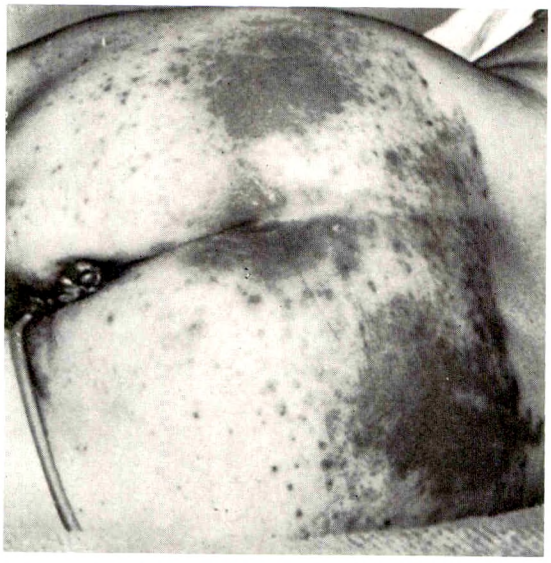


Fig. 5. Carcinoma of the bowel. Bilateral hypogastric artery infusion of FUDR. Note that the local toxicity that has occurred (erythema and skin ulceration) is confined to the distribution of the vessels infused.

Complications of technique of catheter insertion and maintenance of infusion assembly have been frequent and often serious. These consisted of inaccurate catheter placement (11 patients), infection and bleeding, or both, around the tract of the catheter (15 patients) and leakage of infusate (12 patients). These complications have been minimized by using more refined techniques, as recently described.[11]

The increased local biologic effects noted with arterial infusion chemotherapy and the marked antitumor effects that have been observed are attributed to (1) the arterial route of administration, producing a higher local concentration of the drug, and (2) the continuous 24 hour administration of the antitumor drug, resulting in a continuous antimetabolic effect so that slowly metabolizing cells may be affected by the continuous exposure of the antimetabolite as the cells enter an active metabolic phase.

Because of the frequency of complications relating to technique, this form of therapy must be considered to be in the realm of clinical investigation. It is our considered opinion that the casual use of this method of therapy should be discouraged and that its use should be confined to those centers where a program of clinical investigation of this type has been instituted,

with surgeons and chemotherapists actively participating in a concerted effort.

SUMMARY

A program designed to uncover all possible biologic effects of cancer chemotherapeutic compounds in which the agents are administered by prolonged intravenous and intra-arterial administration is reported. The drugs are given by continuous 24 hour intravenous and intra-arterial infusion until maximum local and systemic effects are obtained.

These clinical studies have shown that the prolonged intravenous administration of several cancer chemotherapeutic compounds may alter in a quantitative manner the toxic and therapeutic effects, as well as modify the metabolic fate of these compounds.

Prolonged arterial administration of Mtx and certain fluorinated pyrimidines has resulted in enhanced local antimetabolic and antitumor effects. Partial and, at times, total and sustained tumor regression has been noted. Techniques, complications and results of therapy are described. This method of regional chemotherapy is considered as in the area of clinical investigation. Results to date suggest that this technique of drug administration may in the future become a practical addition to recognized forms of treatment in the management of advanced cancer.

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THE PULMONARY MANIFESTATIONS AND COMPLICATIONS OF LEUKEMIA*

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AN ABNORMAL chest roentgenogram of a patient with known leukemia is common. The radiologist is frequently faced with the decision as to whether the abnormality is a manifestation or one of the complications of the disease. Considerable emphasis is placed on the roentgenographic examination since symptoms, signs, and laboratory data are frequently of little help.

MATERIAL

The clinical records, roentgenograms, and autopsy findings of all proven cases of leukemia seen at Indiana University Medical Center from 1952 through 1959 were reviewed. This period of time was selected because during these years, modern chemotherapy, radiation therapy and antibiotic treatment were utilized. The results of this study would thus be applicable to similar cases currently seen. A total of 341 cases were studied. Autopsies were performed on 121. The number of patients in each category is summarized in Table I.

It will be noted that there is a high percentage of cases with acute lymphocytic, acute myelogenous, and monocytic leukemia. This reflects the tendency of physicians to refer such patients to an institution of this type.

LEUKEMIC MANIFESTATIONS

A review of the literature revealed that relatively little had been written on this important subject. Vieta and Craver[22] briefly mention the roentgenologic findings in chronic lymphocytic and myelogenous leukemia in their classic article, and Falconer and Leonard[7] reported the roentgenographic and autopsy studies on 40 patients with lymphocytic leukemia. A few articles in the English literature have been found in which the pulmonary pathologic findings in leukemia are discussed.[14,18,19] A number of foreign articles[1,2,3,4,6,8,9,16,20,21,23] on the pulmonary pathologic findings in leukemia have been written; however, these were mainly based on a small number of cases.

The leukemic manifestations which are considered here are mediastinal and hilar lymphadenopathy, leukemic infiltrations of the lung, and pleural fluid.

MEDIASTINAL AND HILAR LYMPHADENOPATHY

At autopsy, hilar and mediastinal lymph node enlargement was found in 50 per cent of our cases. It was seen most often in cases of chronic myelogenous (60 per cent), monocytic (57 per cent), and acute lymphocytic (56 per cent) leukemia. It was uncommon in chronic myelogenous leukemia. Roentgenographically, however, mediastinal lymphadenopathy was diagnosed in only 7 per cent of the cases and hilar lymphadenopathy in 10 per cent, being most common in chronic lymphocytic and acute lymphocytic leukemia (Table II). It is of interest that this

TABLE I

LEUKEMIA CASES STUDIED FROM 1952 THROUGH 1959

	Autopsy	Total
Acute Lymphocytic	43	105
Chronic Lymphocytic	20	81
Monocytic	27	81
Acute Myelogenous	9	13
Chronic Myelogenous	15	51
Leukemic Reticuloendotheliosis	7	10
Total	121	341

* From the Departments of Radiology, Internal Medicine, and Pathology, Indiana University Medical Center, Indianapolis, Indiana.

Table II

ROENTGENOGRAPHIC EVIDENCE OF LYMPHADENOPATHY

	Acute Lymphocytic Leukemia 105	Chronic Lymphocytic Leukemia 81	Monocytic Leukemia 81	Acute Myelogenous Leukemia 13	Chronic Myelogenous Leukemia 51	Leukemic Reticuloendotheliosis 10	Total 341
Mediastinal	14%	7%	2%	—	—	—	7%
Hilar	13%	15%	7%	—	2%	10%	10%

is a smaller percentage than that reported by other authors. Vieta and Craver[22] found that 36 per cent of their patients with lymphocytic leukemia had roentgenographically demonstrable mediastinal lymphadenopathy and 27 per cent had hilar lymphadenopathy. Kirklin and Hefke[13] reported 21 per cent with mediastinal lymphadenopathy. The decreased incidence in our series may reflect the changing roentgenographic picture due to the use of modern chemotherapeutic agents.

The most common abnormal roentgenographic pattern was bilateral mediastinal lymphadenopathy with clear demarcation between the lymph nodes so that there was scalloping of the margins. The lymph nodes can enlarge rapidly (Fig. 1, *A* and *B*), sometimes in as short a period as 2 weeks. They usually decreased to normal size within a 1 to 2 month period after the institution of chemotherapy (Fig. 2, *A* and *B*). Occasionally, the mediastinal enlargement would be diffuse with smooth margins (5 cases). This pattern was particularly noted in cases of acute lymphocytic leukemia. It was of interest that there were but 2 patients who had tracheal compression (one of these also had superior vena caval obstruction), and both had diffuse widening of the mediastinum (Fig. 3, *A* and *B*).

The enlarged hilar lymph nodes were usually discrete and bilateral; however, in 7 patients the lymph nodes were not discrete and 3 of these had only unilateral hilar lymphadenopathy which was indistinguishable from that seen in cases of bronchogenic carcinoma.

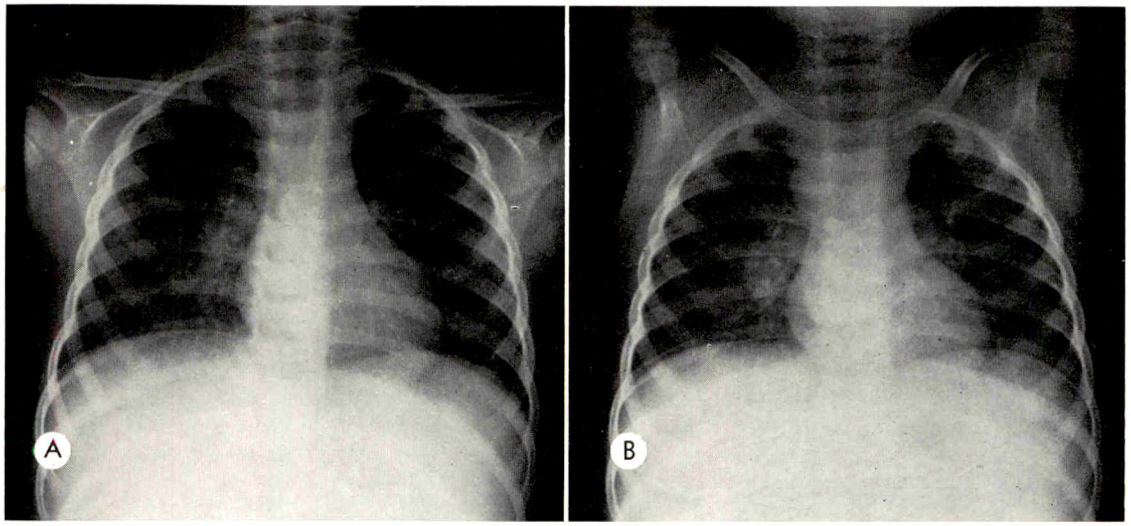


Fig. 1. (*A* and *B*) This 3 year old girl had acute lymphocytic leukemia. Note the increase in mediastinal and hilar lymphadenopathy which occurred in a 4 week period. The hilar and mediastinal lymph nodes are discrete.

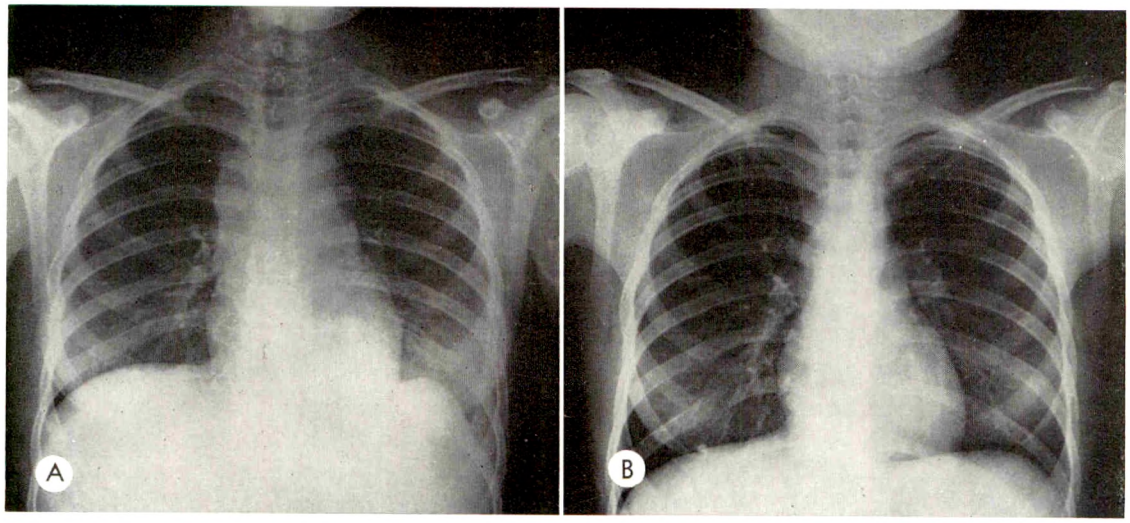


FIG. 2. (*A* and *B*) This 10 year old male had acute lymphocytic leukemia. Note the disappearance of mediastinal lymphadenopathy after 4 weeks of aminopterin therapy. The fact that most patients in this series were on continued chemotherapy may account for the smaller percentage showing mediastinal and hilar lymphadenopathy.

LEUKEMIC INFILTRATIONS

At autopsy, leukemic infiltrations of the lung were found in 31 per cent of the cases (Table III). These were most common in monocytic leukemia (46 per cent) and least common in chronic myelogenous leukemia (15 per cent). The lesions were usually microscopic and several patterns were observed. Most often infiltration of the interalveolar septa with separation of the capillaries from the alveolar walls was found (Fig. 4). Perivascular and peribronchial

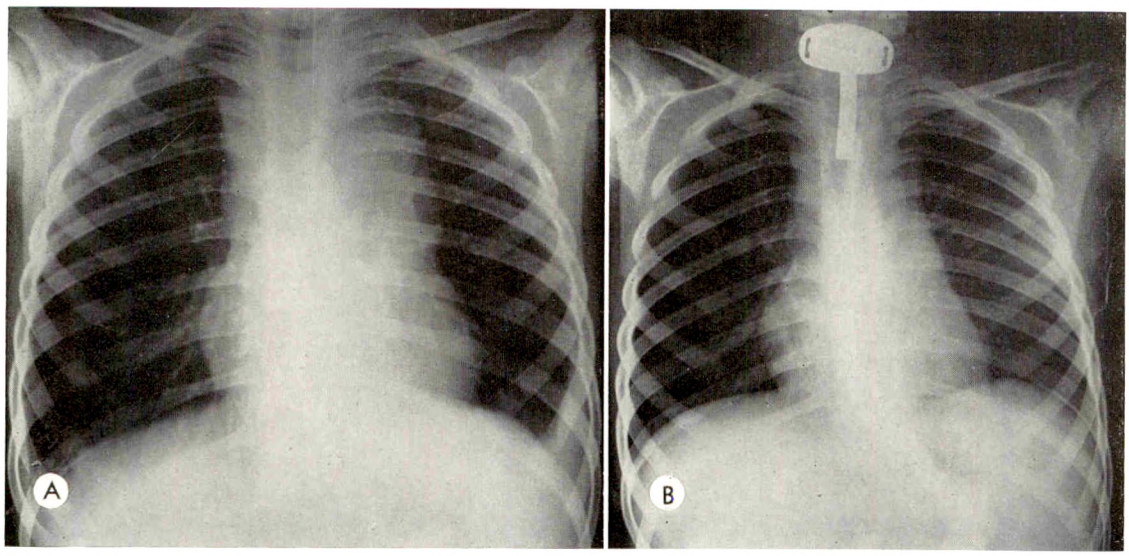


FIG. 3. (*A* and *B*) This 7 year old male had acute lymphocytic leukemia with severe dyspnea secondary to tracheal compression for which a tracheotomy was performed. Note that the mediastinum is diffusely enlarged with smooth margins. There was a dramatic decrease in mediastinal size in a 2 week period following the administration of 300 r to the mediastinum. Emergency radiation therapy may be lifesaving in this group of patients.

infiltrations of leukemic cells were frequently noted. In other cases, the arterioles, capillaries, and venules were dilated and filled with leukemic cells. There frequently was occlusion of the smaller vessels with small infarcts scattered throughout the lungs. Occasionally, the infarcts would be several centimeters in size, and grossly and roentgenographically would appear as pulmonary nodules. The periphery of the infarcts would usually be invaded by leukemic cells (Fig. 5). The etiology of the increased frequency of small pulmonary infarcts is not known. It may be the result of vascular injury by the leukemic process with secondary thrombus formation. Increased viscosity of the blood secondary to the high white blood cell count has been suggested,[19] but there was no correlation between the level of the white blood cell count and the presence of infarcts.

Of 33 cases with leukemic infiltration demonstrated at autopsy, only 7 had roentgenographically demonstrable disease. This was usually manifested as a diffuse peribronchial infiltration which was not localized to a specific segment or lobe (Fig. 6). Nodular lesions of the lung parenchyma were unusual roentgenographic manifestations, being noted in 4 cases of the total series, and in only 1 case with autopsy confirmation. In this case the nodules represented pulmonary infarctions of the lung (Fig. 7). Cavitation of a leukemic lesion as described by others[6,8] was never demonstrated on roentgenograms in this series, nor was leukemic consolidation of a lobe observed pathologically.

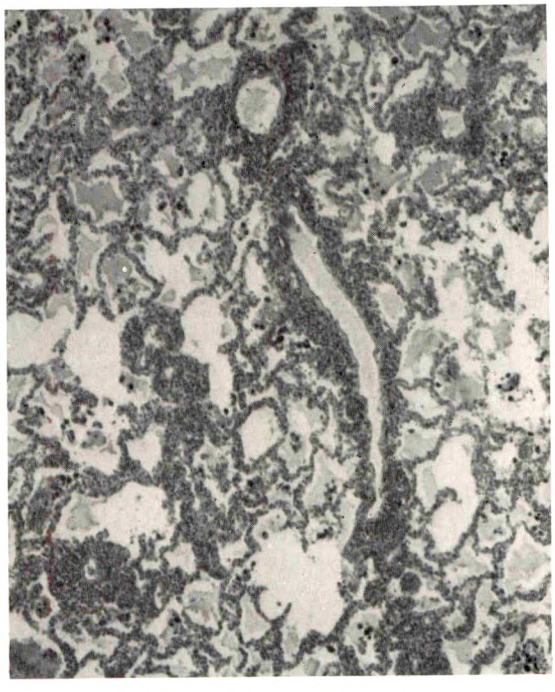


Fig. 4. Interstitial involvement of the lung in leukemia. The round and elongated spaces bordered by a zone of densely packed, darkly staining cells are blood vessels. The leukemic cells tend to collect around tubular structures such as blood vessels and bronchioles. Low magnification photomicrograph.

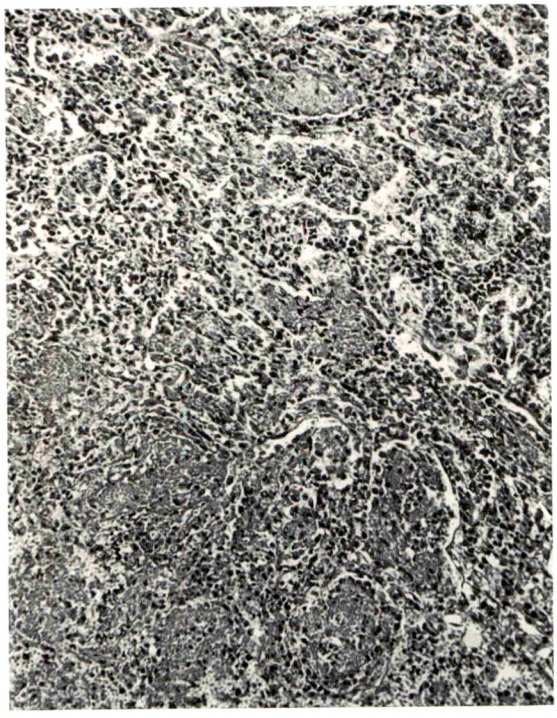


Fig. 5. Infarct of the lung in leukemia. The left, lower half of the figure represents an infarct in which the alveolar walls remain as eosinophilic shadows. Each alveolus contains fibrin in which the few cells present are leukemic. Moderate magnification photomicrograph.

PLEURAL FLUID

Pleural fluid of over 100 cc. was found in 20 per cent of patients at autopsy (Table III). It was most often found in cases of chronic myelogenous leukemia. Gross

TABLE III

AUTOPSY FINDINGS IN LEUKEMIA CASES

	Acute Lymphocytic 43	Chronic Lymphocytic 20	Monocytic 27	Acute Myelogenous 9	Chronic Myelogenous 15	Leukemic Reticuloendotheliosis 7	Total 121
Hilar and Mediastinal Lymph Nodes	56%	44%	57%	13%	6%	57%	50%
Leukemic Infiltration	32%	33%	46%	27%	15%	29%	31%
Infarct	9%	22%	18%	7%	5%	28%	14%
Pleural Involvement	—	11%	4%	—	10%	—	4%
Pleural Fluid (over 100 cc.)	7%	40%	21%	27%	20%	14%	20%
Pneumonia	34%	22%	32%	20%	40%	29%	31%
Atelectasis	10%	—	11%	—	30%	—	11%
Myocardial Infiltration	17%	22%	32%	13%	10%	—	18%
Pericardial Fluid (over 25 cc.)	15%	44%	21%	27%	25%	—	21%

pleural invasion was rare (4 per cent) (Table III). There was frequently noted to be mottled bluish discoloration of the pleura, which on microscopic section appeared to be caused by subpleural infarcts with surrounding leukemic infiltration. Pleural fluid was roentgenographically demonstrable in 11 per cent of the patients (Table IV). It was bilateral in 5 per cent, unilateral on the left in 3 per cent, and unilateral on the right in 3 per cent. It was usually seen in patients with mediastinal lymph node enlargement. It appears possible that, due to the altered morphology of the lymph nodes in these patients, there may be some obstruction to pleural lymphatic drainage.

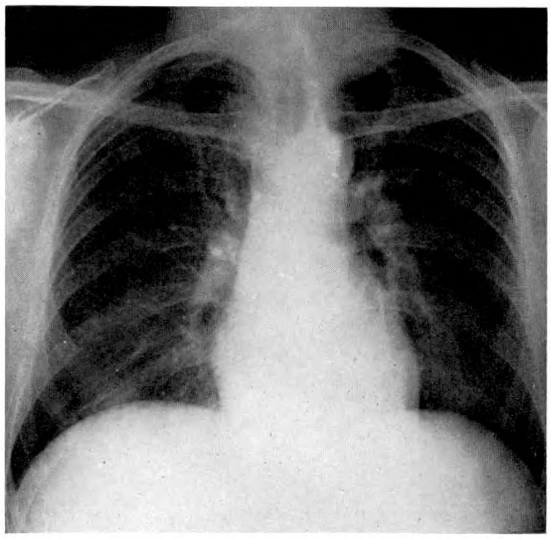


FIG. 6. This 50 year old male had monocytic leukemia and leukemic infiltrations of the lung. Note the diffuse paravascular infiltrations which give the lung fields a reticular appearance. This was the most common pattern noted.

TABLE IV

ROENTGENOGRAPHIC FINDINGS IN LEUKEMIA CASES

	Acute Lymphocytic 105	Chronic Lymphocytic 81	Monocytic 81	Acute Myelogenous 13	Chronic Myelogenous 51	Leukemic Reticuloendotheliosis 10	Total 341
Normal	50%	40%	51%	46%	73%	40%	51%
Mediastinal Lymphadenopathy	14%	7%	2%	—	—	—	7%
Hilar Lymphadenopathy	13%	15%	7%	—	2%	10%	10%
Pulmonary Infiltrations	21%	42%	29%	8%	14%	40%	30%
Infarct	—	1%	1%	—	—	—	1%
Pleural Fluid Bilateral	3%	10%	2%	8%	2%	10%	5%
Left	3%	2%	5%	—	—	—	3%
Right	2%	5%	4%	—	2%	—	3%
Total	8%	17%	11%	8%	5%	10%	11%
Atelectasis	—	2%	—	—	—	10%	1%
Cardiomegaly	25%	4%	16%	10%	10%	10%	16%
Pericardial Effusion	1%	1%	1%	—	—	—	1%
Pulmonary Congestion	13%	5%	11%	12%	12%	10%	12%
Nodules	17%	1%	2%	—	—	—	1%

COMPLICATIONS

PNEUMONIA

The development of pneumonia as a complication of the terminal state of leukemia is well known. This entity was present in 31 per cent of our autopsied cases, being most frequent in chronic lymphocytic leukemia (40 per cent), and least frequent in chronic myelogenous leukemia (20 per cent) (Table III). Pulmonary infiltrations were demonstrable roentgenographically in 30 per cent of the entire series and were most frequently noted in chronic lymphocytic leukemia (42 per cent) (Table IV). Pneumonia was not present in every case which demonstrated pulmonary infiltration; however, after a review of the clinical course, bacteriologic studies, and response to antibiotic therapy, it was concluded that the vast majority of these infiltrations did indeed represent pneumonic processes. These

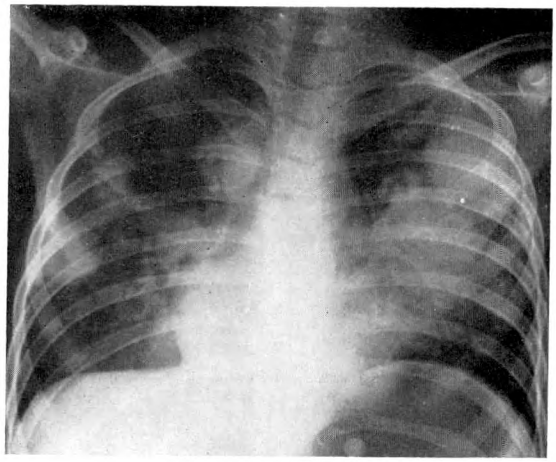


FIG. 7. This 12 year old female had monocytic leukemia with nodular lesions in both lungs which, at autopsy, were found to represent pulmonary infarcts with leukemic infiltrations at the periphery of the infarct.

infiltrations were either parabronchial or homogeneous consolidations and were usually limited to a single lobe (Fig. 8). This might be a differential point in distinguishing from leukemic infiltrations which, in this series, were usually generalized.

The pathogenesis of infectious complications in the course of leukemia has not been resolved. However, Hudson and Sloan[10] reported the finding of hypogammaglobulinemia in 68 per cent of 40 unselected cases of chronic lymphocytic leukemia. In 11 patients with normal gamma globulin values, 14 infectious processes occurred. They further reported no significant variation from normal of gamma globulin values in 18 patients with chronic myelogenous leukemia and in 11 patients with acute leukemia. This study correlates well with our finding that the highest incidence of pulmonary infections occurs in chronic lymphocytic leukemia.

It has further been noted clinically that infectious complications are particularly likely to accompany a leukopenic state of any given case of leukemia. For this reason, it is the policy at this institution to administer antibiotics to all patients who demonstrate a white blood cell count below 2,000.

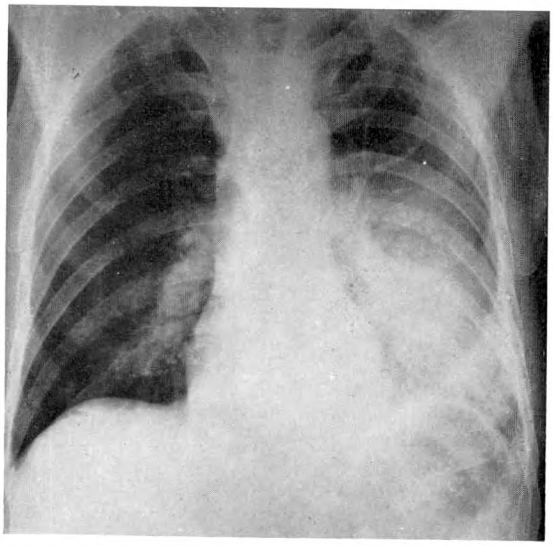


FIG. 8. This 63 year old white male had monocytic leukemia and lobar pneumonia. In our series, leukemic infiltrations did not show this appearance.

FUNGAL DISEASES

The increased incidence of fungal disease in patients with leukemia or lymphoma has been reported by a number of authors.[5,12,24,25] Zimmerman and Rappapart[25] reviewed 74 cases of cryptococcosis at the Armed Forces Institute of Pathology and noted that 24 of these were infections that complicated a lymphoma or leukemia. Zimmerman[24] stated that widespread infection is generally unusual in cryptococcosis, but when the infection occurs in a patient with lymphoma or leukemia, widespread and disseminated lesions are the rule. Keye and Magee[12] found that the occurrence of fungal disease was common after 1947 but rare prior to this time. In 1954 and 1955, 20 per cent of their patients with leukemia or lymphoma had complicating fungal infections. It was their opinion that the increased incidence of fungal disease in leukemic patients was a result of therapy with multiple antibiotics, chemotherapeutic agents used in the treatment of leukemia and lymphoma, and cortisone.

In our series, 3 patients had disseminated fungal disease. One patient had crypto-

coccosis (Fig. 9), 1 had histoplasmosis (Fig. 10), and 1 had blastomycosis. All 3 patients had chronic lymphocytic leukemia.

TUBERCULOSIS

There has been a difference of opinion as to the association of tuberculosis and leukemia. It would appear reasonable that due to the leukemic process, the resistance of the patient to any infectious disease would be weakened, and therefore stable tuberculosis might be reactivated or the patient might be more susceptible to contact with the disease organism. Kirshbaum and Preuss,[14] in a study of autopsy material of 123 cases of leukemia, found 16 cases of active tuberculosis. They stated that this was not statistically significant. Lowther[15] reviewed the postmortem findings of 27,104 patients. Tuberculosis was found in 5.6 per cent of patients with leukemia as compared to 6.5 per cent in the total group. Tuberculosis was associated with all types of leukemia but was most often found in chronic myelogenous leukemia.

Although there may be no statistical increase of tuberculosis with leukemia, tuberculosis must always be considered in any patient with pulmonary infiltration. Active tuberculosis was discovered in 7 patients. Six of these patients had chronic lymphocytic leukemia and 1 had chronic myelogenous leukemia. Three patients had known arrested tuberculosis prior to the diagnosis of leukemia, which later became active (Fig. 11). The other 4 patients had no previous history of tuberculosis (Fig. 12). The correct diagnosis in this group of patients is important since steroid therapy may disseminate the disease.

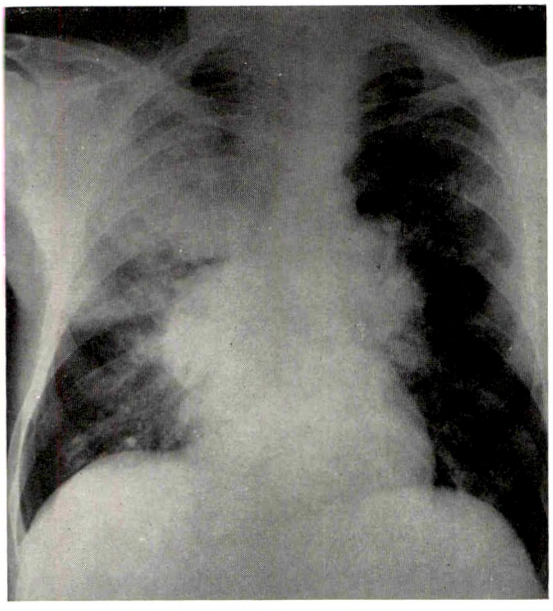


Fig. 9. This 53 year old white male had chronic lymphocytic leukemia and disseminated cryptococcosis.

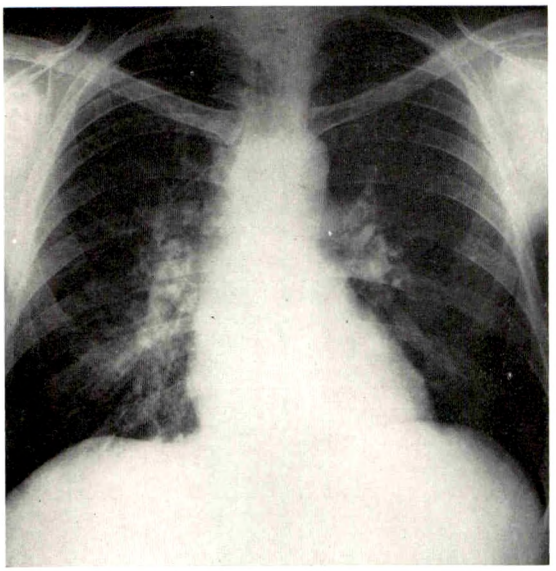


Fig. 10. This 66 year old white male had chronic lymphocytic leukemia and disseminated histoplasmosis. Note the fine miliary densities which proved to be small granulomas.

Another point which should be made is that some patients with disseminated tuberculosis may have a leukemoid reaction which is difficult to differentiate from leukemia. The reaction may involve any cell type.[11] In any patient with a miliary infiltration of the lungs, it is hazardous to accept the diagnosis of leukemic infiltration. In our entire series, there was only 1 patient with leukemic infiltrations which had a roentgenographic appearance similar to that of miliary tuberculosis (Fig. 13). Miliary tuberculosis, either as a complication of leukemia or with a leukemoid reaction, should be strongly considered.

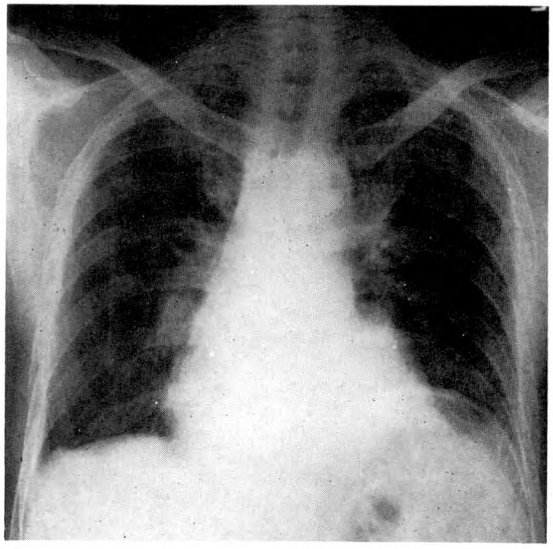


FIG. 11. This 51 year old white male had chronic lymphocytic leukemia diagnosed in 1956. In 1955 he was found to have active pulmonary tuberculosis. This became stable on antituberculous therapy. In 1960, he developed soft infiltrations in both upper lobes and the sputum was positive for acid fast bacilli.

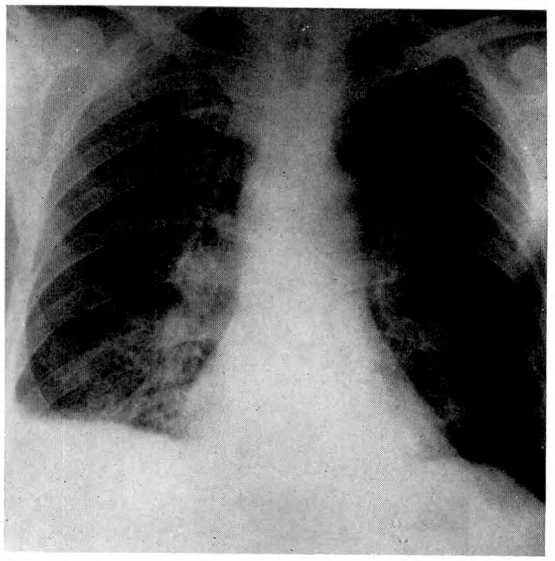


FIG. 12. This 64 year old white male had leukemic reticuloendotheliosis. Miliary lesions of the lungs were noted and misinterpreted as leukemic infiltrations. At autopsy, disseminated tuberculosis was found.

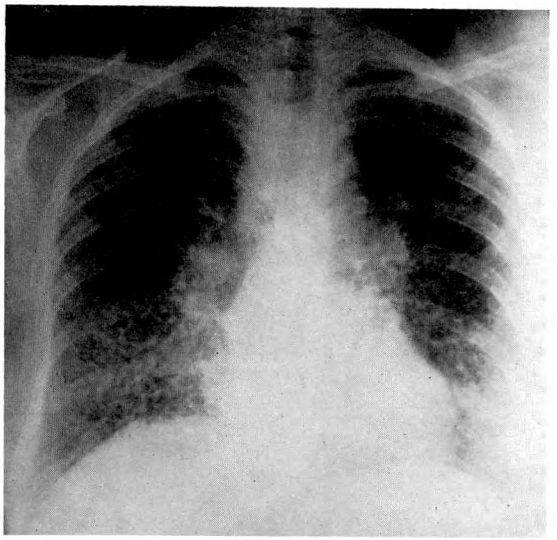


FIG. 13. This 47 year old white female had chronic lymphocytic leukemia. Miliary lesions in both lungs were noted which progressed in size and number. Numerous sputa were negative for tuberculosis, histoplasmosis, and malignant cells. Skin tests for fungi and tuberculosis were negative. Complement fixation tests for fungi were normal. Bronchoscopy was normal. Although there is no autopsy confirmation, the lesions are thought most likely to represent leukemic infiltrations. This was the only case in this series in which the leukemic infiltrations of the lung resembled those of miliary tuberculosis.

CARDIOMEGALY AND CONGESTIVE HEART FAILURE

Cardiac enlargement and pulmonary congestion were noted often (16 per cent and 12 per cent) (Table IV). These were particularly observed in children with acute leukemia and in elderly patients with either acute or chronic leukemia. At autopsy, leukemic infiltration of the myocardium was present in 18 per cent of the patients (Table III), but there was no correlation between myocardial leukemic infiltrations and cardiomegaly and congestive heart failure. Cardiomegaly and congestive heart failure were almost always associated with a hemoglobin below 5 gm. per cent. Because of the decreased amount of oxygen carrying hemoglobin and the increased metabolism of a patient with leukemia, cardiac output may be greatly increased and congestive failure may develop. Roentgenographically, pulmonary congestion may be misinterpreted as leukemic infiltration or pneumonia. This pattern would usually return to normal following blood transfusion (Fig. 14, *A* and *B*). Pericardial effusion of over 25 cc. was found

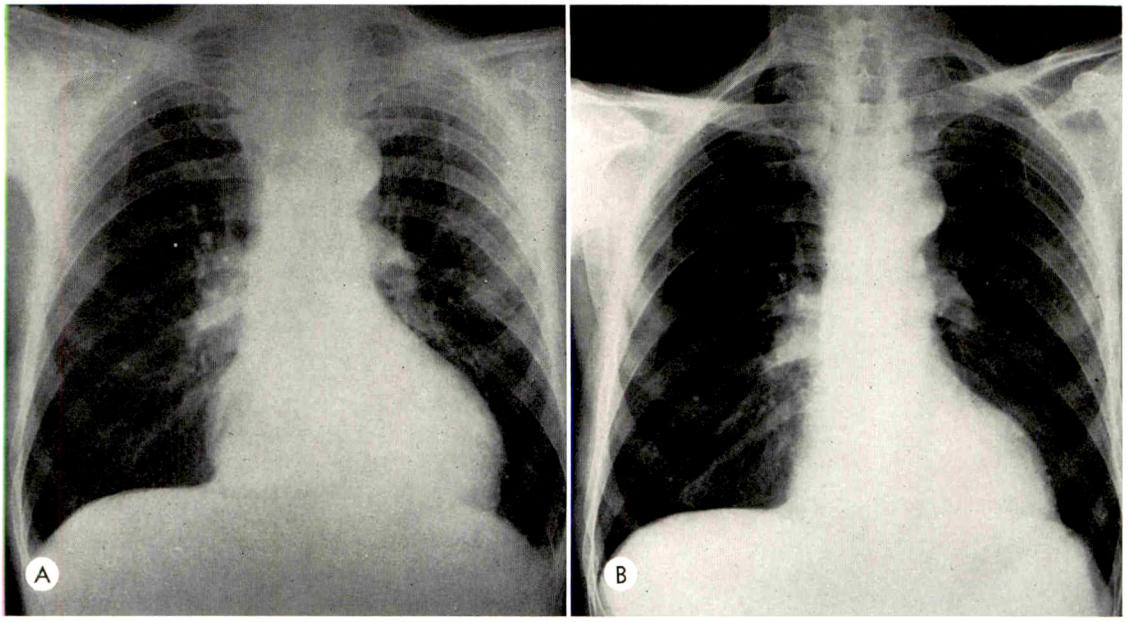


Fig. 14. (*A* and *B*) This 70 year old white male had monocytic leukemia. Note the decrease in cardiac size which corresponded with the increase in hemoglobin from 8 gm. to 12 gm.

in 21 per cent of the patients at autopsy (Table III). It was unusual for pericardial effusion to exceed 100 cc. Because of the small amount of pericardial fluid, pericardial effusion was rarely diagnosed on roentgenographic studies (1 per cent) (Table IV).

ATELECTASIS

Lobar atelectasis was found in 11 per cent of the series on autopsy examination. This was particularly common in chronic myelogenous leukemia (30 per cent) (Table III). It was frequently associated with pleural effusion so that the roentgenographic diagnosis was made in only 1 per cent (Table IV).

OTHER MALIGNANCY

The presence of one malignant process does not exclude another.[17] The following case is reported to demonstrate this occurrence.

This 73 year old male was first seen on October 16, 1953 with an ulcerated lesion of the cheek and nose. Biopsies were interpreted as epidermoid carcinoma. At the same time, the patient was discovered to have chronic lymphocytic leukemia. In 1958, a right hilar mass developed. This gradually increased in size over a 6 month period (Fig. 15, *A*, *B* and *C*). At autopsy, the patient was found to have an epidermoid carcinoma of the right lobe, adenocarcinoma of the prostate, adenocarcinoma of the ascending colon, and carcinoma *in situ* involving a polyp of the descending colon.

It was of interest that 11 other patients had multiple malignancies (excluding skin). The types of lesions were malignant melanoma, carcinoma of the soft palate, carcinoma of the larynx, carcinoma of the pharynx, carcinoma of the common bile duct, carcinoma of the rectum, carcinoma of the prostate (2), carcinoma of the cervix, retinoblastoma, and meningioma.

SUMMARY

1. The autopsy and roentgenographic intrathoracic manifestations of leukemia are summarized in Tables III and IV.

2. With present day therapy, intrathoracic manifestations of leukemia are rare. Hilar and mediastinal lymphadenopathy and pleural fluid were the most frequent findings. Leukemic pulmonary lesions were unusual and in this series were most often

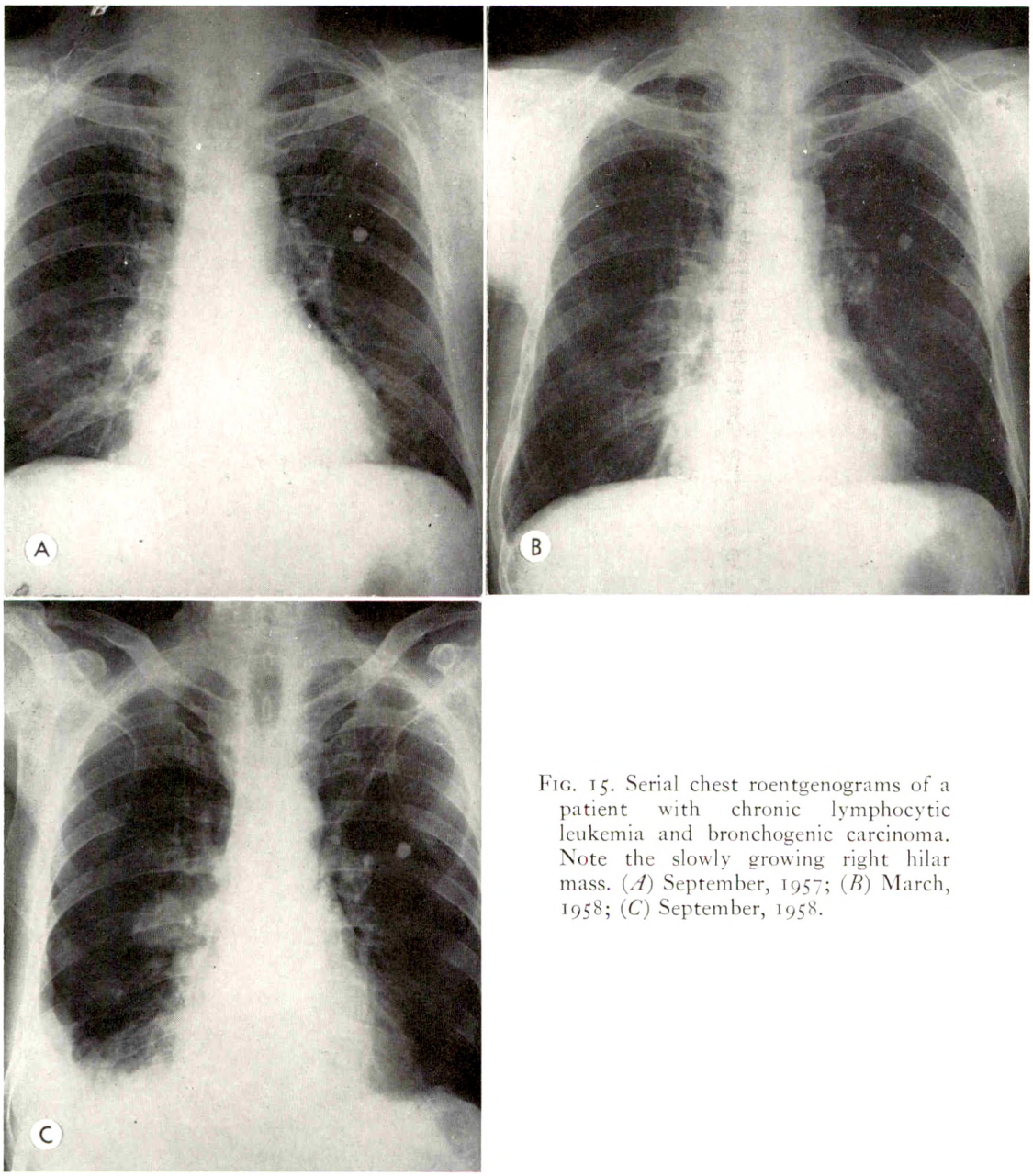


Fig. 15. Serial chest roentgenograms of a patient with chronic lymphocytic leukemia and bronchogenic carcinoma. Note the slowly growing right hilar mass. (*A*) September, 1957; (*B*) March, 1958; (*C*) September, 1958.

characterized by diffuse paravascular infiltrations. Localized infiltration in a lobe of the lung was not observed. Nodular lesions are occasionally seen and usually represent pulmonary infarctions.

3. Pneumonia is quite common in patients with leukemia, particularly in those with the chronic lymphocytic variety.

4. There is an increased incidence of disseminated fungal diseases in leukemia. This may be secondary to the use of antibiotic and chemotherapy for leukemia.

5. Tuberculosis, although not statistically increased in patients with leukemia, should always be considered in any patient with pulmonary infiltration, particularly of a miliary type. Lobar atelectasis was found in 11 per cent of the series at autopsy, but

was only rarely demonstrable roentgenographically because of its resemblance to pleural effusion.

6. Congestive heart failure is also a frequent complication. It is almost always associated with severe anemia.

7. It is a common error to misdiagnose one of the complications of leukemia as a manifestation of leukemia due to an unconscious association of cause and effect.

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ACUTE MYELOGENOUS LEUKEMIA COMPLICATING RADIOACTIVE IODINE THERAPY OF THYROID CANCER*

REPORT OF A CASE

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THE question of leukemogenesis in man by ionizing radiation is one of general interest. Patients with metastatic thyroid cancer treated with radioactive iodine may survive for a considerable number of years and thus provide an opportunity for assessing in man relatively long term biologic effects of substantial amounts of radiation from an internally deposited radioactive substance. We wish to present here the clinical, hematologic, and pathologic findings of a patient with highly functioning, well differentiated metastatic thyroid carcinoma who received a total of 805 mc of I^{131} therapeutically over a 4 year period. The estimated total radiation dose to the blood was 1,600 rads. Total biologically effective radiation dose to bone marrow was estimated to be about 44 per cent of the radiation dose to the blood. The patient developed an acute myelogenous leukemia of the "aleukemic" variety which terminated fatally.

REPORT OF A CASE

The patient (R.T., Brookhaven National Laboratory Hospital No. 3320R, born April 13, 1895), a white housewife 58 years of age at the time of death on December 18, 1953, first noted an anterior cervical mass in 1933. She remained otherwise asymptomatic until right hip pain appeared in 1947. A pathologic fracture of the right femoral neck was discovered and was nailed in 1948.

In 1949 aspiration biopsies of the cervical mass and a mass involving the right ilium were diagnosed pathologically as "benign metastasizing struma." During the remainder of her illness she was followed at Memorial Hospital, New York City and at Brookhaven National Laboratory Hospital, Upton, New York. At the time of her first admission to the Brookhaven Hospital in October, 1949, her principal symptoms were right hip pain, virtual inability to walk, anorexia, nervousness, and generalized weakness. Aside from the present illness, the history was not remarkable. On physical examination a 1.5×2 cm. hard solitary nodule was palpable adjacent to the right lobe of the thyroid. A large subcutaneous mass, quite firm in consistency, extended from the right iliac crest to the right groin. A subcutaneous mass of similar consistency overlay the right femoral greater trochanter beneath a 5 inch vertical surgical incision scar. The liver and spleen were not palpable and there was no lymphadenopathy. The vital signs were within normal limits and the remainder of the physical examination was not remarkable. Admission skeletal roentgenograms showed extensive destructive metastatic lesions in the pelvic bones and proximal right femur.

In January, 1950, a surgical total thyroidectomy was performed. The pathologic diagnosis of the surgical specimen was Hürthle cell carcinoma. Subsequent symptomatic hypoparathyroidism with tetany was satisfactorily controlled by supplementary vitamin D and calcium.

During the patient's numerous hospital admissions in the period 1950–1953, she received a total of 805 mc of therapeutic I^{131}. Details are given in Table 1. The isotope therapies were preceded by withdrawal of desiccated thyroid and prolonged administration of thiouracil (0.5 gm. three times daily) with resultant induction of hypothyroidism or, in some instances, myxedema. I^{131} tracer studies indicated substantial improvement in tumor uptake following periods

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TABLE I

SUMMARY OF I^{131} THERAPY DATA AND RADIATION DOSE ESTIMATIONS

Treatment date	2/3/50	5/10/50	8/17/50	5/18/51	3/21/52	2/20/53	Total
Dose of I^{131} (mc)	50	50	200	182	168	155	805
Cumulative urinary excretion (%)							
24 hours	4.2	7.0	6.4	12.0	13.2	27.6	
48 hours	5.4	8.1	8.7	14.9	16.5	36.3	
Total radiation dose to blood (rads)	122	109	426	410	300	230	1,600
Total radiation dose to tumor (rads)	4,040	3,600	14,200	13,500	11,500	6,670	53,500

of thiouracil administration[14] and satisfactory tumor uptakes of the therapeutic doses obtained in this way were reflected in low values for I^{131} urinary excretion. Therapeutic I^{131} was carrier free and was given orally not less than 48 hours after discontinuing thiouracil. Details of collection and radioactivity assay of blood and excreta and details of estimation of radiation dose to blood, bone marrow, and tumor are given elsewhere. When the factors of biologic recovery from radiation during the period of radiation exposure, beta energy absorption by bone trabeculae, and the probable inequality of blood and bone marrow concentrations of isotope were taken into account, it was estimated that the biologically effective combined beta and gamma radiation dose to bone marrow was about 44 per cent of the total physical radiation dose to the blood.[6] Accordingly, the total biologically effective radiation dose to bone marrow from the six therapies combined is estimated to be about .44(1,600) = 704 rads (Table I).

In the periods between therapies when no thiouracil was being given, symptoms of hypometabolism were alleviated by desiccated thyroid up to 90 mg. daily. No acute hematologic complications clearly attributable to thiouracil administration were observed.

Hematologic examinations were carried out using standard clinical laboratory methods. Platelet counts were made by a chamber technique. The number of a particular type of leukocyte per $mm.^3$ of blood was calculated from the total white blood cell count and the differential count of a Wright stained blood smear. Hematologic observations made over the 4 year therapy period are presented graphically in Figure 1, where the times of administration and dosage of therapeutic I^{131} are also indicated. The leukocyte values plotted in Figure 1 represent the mean of 2 to 4 (usually 3) consecutive determinations. The results of the 4 bone marrow examinations which were performed are presented in Table II.

During the last 4 years of the patient's course, repeated skeletal and chest roentgenograms and physical examinations showed no evidence of cervical recurrence of tumor. No lesions other than those of the pelvis and right femur were observed. These lesions were visible on the 1949 roentgenograms and in the next 4 years increased in size slowly and only to a moderate degree.

The patient's principal symptoms over the 4 years of observation were essentially those present at the time of the first admission. About 1 week following administration of therapeutic I^{131} in August, 1950, the patient developed herpes zoster in the distribution of the left sixth intercostal nerve. Her last dose of therapeutic I^{131} was given on February 20, 1953 (see Fig. 1) and at the time of her discharge home on April 3, 1953 she was doing moderately well.

About June, 1953, the patient observed progression of anorexia, pelvic pain, and weakness, leading to readmission to the hospital on September 9, 1953. At this time the pallor of the skin and mucous membranes was striking. Hematologic examination revealed a clear cut pancytopenia (Fig. 1). The tourniquet test was markedly positive. A gastric analysis showed free hydrochloric acid. A sternal marrow aspiration performed on September 14, 1953 showed scanty material and sparse nucleated elements (Table II). Smudge forms were present in a ratio of 1:1 with normal elements. There was a reduction in the granulocytic series with little maturation. The lymphocytes were increased.

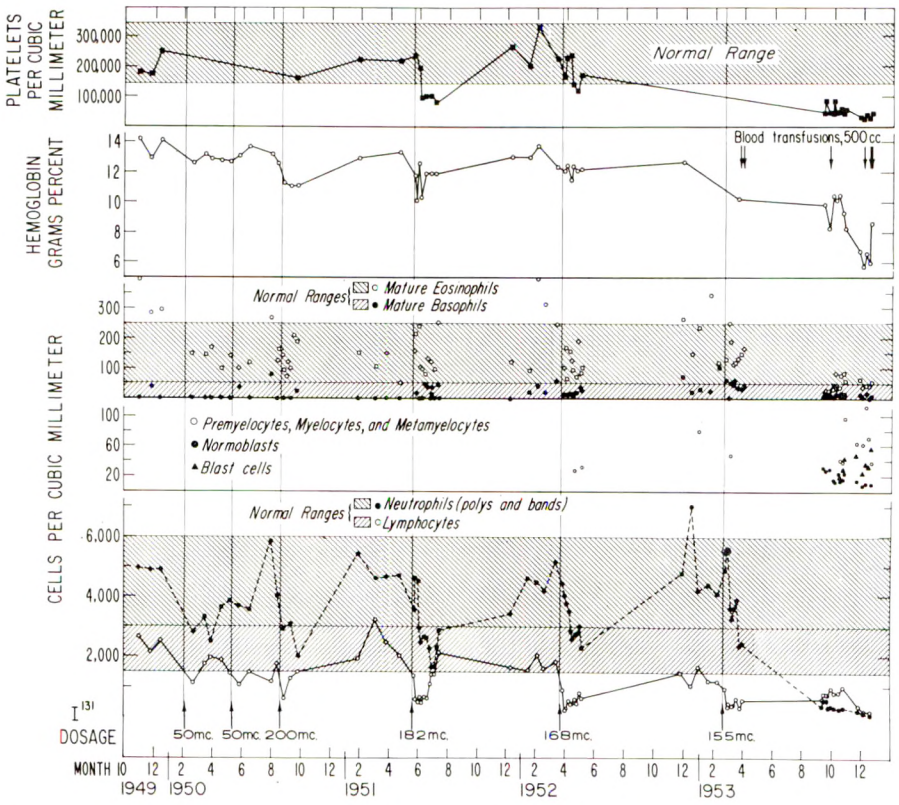


FIG. 1. Graphic presentation of serial hematologic findings. Values for the normal ranges depicted are taken from Wintrobe,[18] pp. 232, 269.

The red blood cell series showed abnormal forms with stippling. The myeloid:erythroid ratio was slightly less than 1. These findings were considered to be consistent with a hypoplastic marrow.

The appearance and progression of what appeared to be bone marrow hypoplasia at a time this late after the last administration of I^{131} were at first puzzling. The "immature granulocytes," indicated by the four points in Figure 1, prior to October, 1953 were myelocytes. However, blast cells and premyelocytes were repeatedly observed on blood smears subsequent to October 14, 1953, suggesting the presence of leukemia.

The patient's condition steadily deteriorated. Numerous petechiae and ecchymoses appeared. A total of 1,400 r of 250 kv. roentgen therapy was given to the pelvic region in the interval from October 29, 1953 to November 17, 1953 in an attempt to relieve her severe pelvic pain. The terminal course was characterized by severe anemia requiring transfusions, persistent granulocytopenia and thrombocytopenia, and repeated infections (laryngitis, stomatitis, and pyelonephritis). Cortisone in doses as high as 300 mg. a day produced no improvement in the blood picture. The terminal episode appeared clinically to be an extensive pneumonia of the right lower lobe which did not respond to antibiotics and blood transfusions. Death occurred on December 18, 1953.

Postmortem Findings. External examination revealed a healed transverse thyroidectomy scar. The right hip area was enlarged by a mass involving the innominate bone. The skin contained generalized petechiae.

Examination of body cavities and organs showed 150 cc. of blood tinged fluid in the right hemithorax. The aorta was prominently involved by calcific atherosclerosis.

The right lung weighed 1,080 gm. The posterior pleural surface was covered by fibrin. There was extensive consolidation of the major portion of the lower lobe and a contiguous portion of the upper lobe anteriorly. The right bronchial tree contained inspissated gastric contents. Section of the lung revealed an extensive reddish

TABLE II

DIFFERENTIAL COUNTS ON ASPIRATED BONE MARROW

Date	5/18/51	6/5/51	6/13/51	9/14/53	Normal* Range	Normal* Mean
	Per Cent					
Myeloblasts				1.0	0.3–5	2
Promyelocytes	1.0	1.0	1.6	5.0	1–8	5
Myelocytes-neutrophilic	12.4	12.0	16.0	9.0	5–19	12
eosinophilic				1.0	0.5–3	1.5
basophilic				2.0	0–0.5	0.3
Metamyelocytes	17.2	18.4	26.0	8.0	13–32	22
Polymorphonuclear neutrophils	27.2	29.8	20.0	4.0	7–30	20
eosinophils	2.0	1.4	1.8		0.5–4	2
basophils		0.2	0.4		0–0.7	0.2
Lymphocytes	8.0	2.6	2.0	22.0	3–17	10
Plasma cells					0–2	0.4
Monocytes	0.6	0.8	0.6	1.0	0.5–5	2
Reticulum cells					0.1–2	0.2
Megakaryocytes		0.2			0.3–3	0.4
Pronormoblasts				2.0	1–8	4
Normoblasts	31.6	33.6	31.6	34.0	7–32	18
Stippled normoblasts				8.0		
Stippled erythrocytes				2.0		
Unidentified				1.0		
Myeloid: Erythroid ratio	1.9	1.9	2.1	0.7	3–4	

* Taken from Wintrobe,[18] p. 61.

consolidation and pronounced edema. The left lung weighed 510 gm. The bronchial tree contained a small quantity of aspirated gastric contents. The lower lobe was congested and edematous. The thyroid area was serially sectioned and no evidence of thyroid or parathyroid tissue was found. The adrenals were severely congested, with dark red cortices. The right and left kidneys weighed 150 and 160 gm., respectively. The cortices showed a fine granularity. The gallbladder contained 2 irregular varicolored stones and the mucosa showed cholesterolosis. The spleen weighed 300 gm. and was soft and diffluent with a slightly thickened capsule. The lymph nodes were not significantly enlarged. The ovaries were small and atrophic.

The right hip region contained a cavity 10 cm. in diameter filled with clear yellow fluid. No tumor was identified grossly. The left acetabular region was explored from within the pelvis. Edematous and hemorrhagic material resembling tumor was encountered. Sections of bone marrow taken from the lumbar vertebrae, ribs and sternum revealed it to be soft and dark brown. All other organs were examined except the brain, pituitary gland and spinal cord and were essentially negative.

Microscopic Examination. Sections of tumor from the left acetabular region revealed dense scar tissue containing scattered carcinoma cells, some of which were arranged in poorly formed follicles containing colloid (Fig. 2). The microscopic picture was considered to be consistent with radiation effect on tumor. Sections taken from skeletal muscle overlying the left acetabular tumor showed occasional muscle cells having greatly enlarged, hyperchromatic nuclei simulating those seen in rhabdomyosarcoma. In this instance, however, the change was attributable to irradiation. Sections of the wall of the right iliac cyst, like the sections of the left acetabular tumor, revealed dense scar tissue containing scattered carcinoma cells, occasionally arranged in poorly formed follicles. The lining of the cyst was markedly congested and hemorrhagic. In some areas it was composed of metaplastic squamous epithelium. Some of the tumor cells showed cytoplasmic vacuolization and brown granules resembling hemosiderin. Sudan IV stains showed some of the vacuolated cells to contain fat.

Multiple sections of bone marrow showed complete loss of the normal architectural pattern with replacement by immature and blast forms of the granulocytic series. Occasional

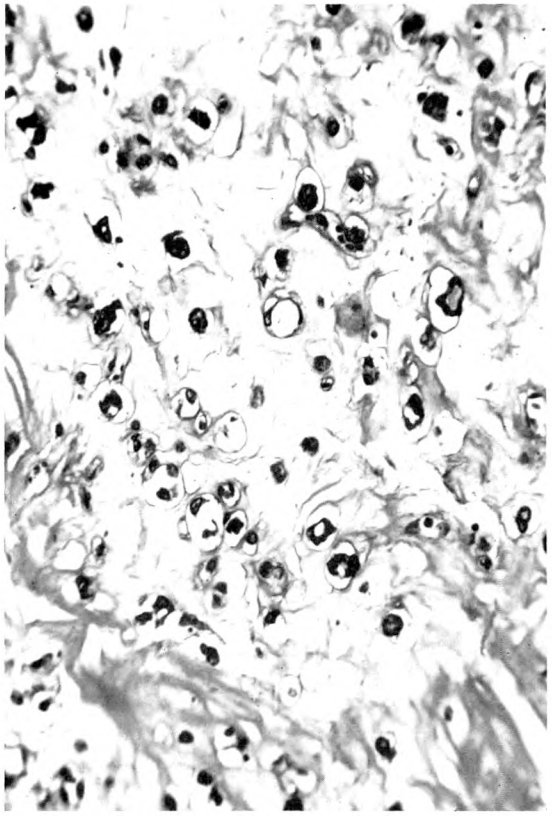


FIG. 2. Section of tumor from left acetabular region showing poorly formed acini. The abnormal nuclei and fibrosis are considered to be due to ionizing radiation.

prophase and metaphase mitotic figures were present. Scattered megakaryocytes were observed. The erythropoiesis was reduced. Occasional granules of brown pigment, presumably hemosiderin, were present. There was cellular pleomorphism as ordinarily found in myelogenous leukemia (Fig. 3).

Sections of spleen revealed loss of the normal architecture with only small foci of lymphocytes remaining. There was replacement by large immature and blast forms similar to those observed in the bone marrow. There were foci of multinucleated giant cells, some of which resembled megakaryocytes. The changes observed were those of myelogenous leukemia (Fig. 4).

Sections of liver showed foci of immature mononuclear cells, apparently blast forms, resembling those observed in the marrow and spleen. Lymph node sections showed loss of the normal pattern with hemorrhage and scattered cells similar to those present in the marrow. The latter were particularly evident about the

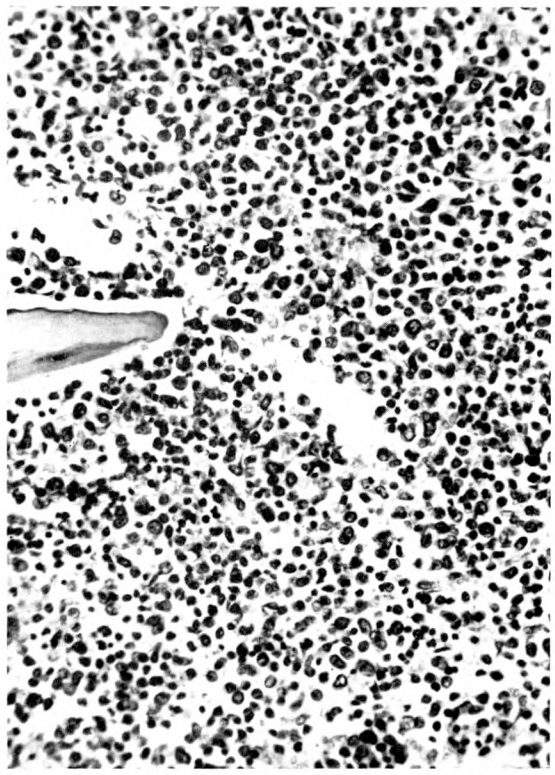


FIG. 3. Bone marrow showing changes of myelogenous leukemia.

capsular areas. There was prominent hemosiderosis.

Sections of the right lung revealed extensive alveolar hemorrhage. There was a scattered mononuclear exudate which resembled immature myeloid elements. The picture was one of pneumonia superimposed on a bleeding diathesis with inadequate mature leukocytes to combat the infection. The kidneys showed nephrosclerosis. The adrenals showed severe congestion and hemorrhages in the cortices. The ovaries were atrophic. Sections of heart showed mild basophilic degeneration.

The sections presented in Figures 2–4 were stained with hematoxylin and eosin.

Principal Final Diagnoses. (1) Thyroid carcinoma, metastatic, showing postradiation changes; (2) myelogenous leukemia, aleukemic, acute; (3) lobar pneumonia, right lung, with extensive hemorrhage; and (4) adrenal cortical hemorrhage.

DISCUSSION

It is of interest that the bodies of data affording statistical evidence that radiation may induce leukemia in man for the most

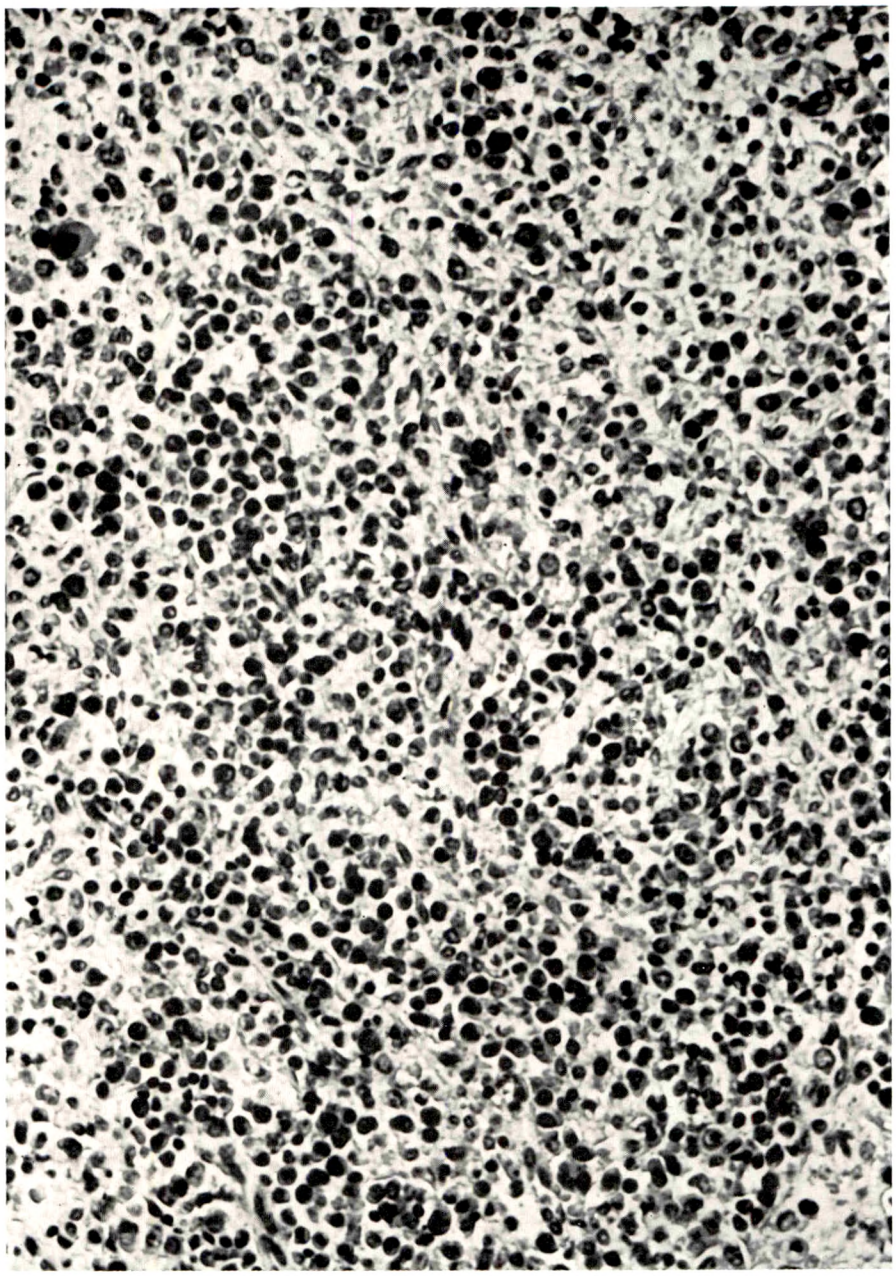


Fig. 4. Spleen showing changes of myelogenous leukemia. (×140.)

part involve penetrating radiation from external sources. This would seem to be the case for the increased incidence of leukemias noted in radiologists,[8] in Japanese survivors of the atomic explosion,[11] and in patients who have received substantial doses of therapeutic roentgen rays for spinal arthritis.[3] The evidence for induction of leukemia by internally deposited radioactive materials in man is meager. Apparently very few cases of leukemia have been reported in humans bearing internally deposited radium. This has been attributed to the fact that at late times after body entry the retained radium is found principally in small areas of high focal concentration irregularly distributed in the skeleton, which would not produce diffuse bone marrow ir-

radiation,[16] and to the limited penetration of the marrow by alpha particles from radium in bone.[15] However, apparently at least 5 cases of leukemia have been observed in patients previously given intravenous or intracavitary thorotrast. Most of this material is retained after administration and is distributed widely in the reticuloendothelial system.[7]

Accumulated cases of the type reported here may prove to be an important source of information relative to the question of human leukemogenesis by substantial amounts of irradiation from internal sources. In this regard, cases of functioning metastatic thyroid cancer considered suitable for radioactive iodine therapy frequently differ in at least two important respects from the various malignancies and blood dyscrasias commonly treated with internally administered radioactive isotopes. First, their life expectancy[12] is often comparable to or better than the latent period of 2 or more years most commonly observed in the cases of leukemia among the Japanese atom bomb survivors and cases of spinal arthritis given roentgen treatment;[11,13] and secondly, there would appear to be no reported tendency of note for the untreated disease to be complicated by leukemia or similar blood dyscrasia.

The present case presents a number of hematologic features worthy of note. There was no clinical or hematologic evidence for the presence of leukemia prior to administration of therapeutic I^{131} (see also Table II). Symptomatically, the onset of leukemia probably could reasonably be considered to have occurred about June, 1953, approximately 40 months after the first dose of therapeutic I^{131}. Despite the absence of findings indicating leukemia in the bone marrow examination of September, 1953, 3 months prior to death, a hematologic diagnosis of leukemia would probably have been justified by the presence of blast cells with other immature forms in the peripheral blood as early as October 14, 1953, or 44 months after initiation of radioactive iodine therapy. These time lapses are consonant with the latent periods following irradiation for induction of human leukemia mentioned above.

Moloney and Lange[9,10] have found that in atomic bomb survivors elevation of absolute basophil counts or the presence of even a small number of immature myeloid cells in the peripheral blood strongly suggest the presence of early myelogenous leukemia. Granulocytosis, relative lymphopenia, and changes in red blood cells such as polychromasia, anisocytosis, and occasional nucleated red blood cells were also frequently observed. Unfortunately in this case accurate absolute basophil counts were not performed. The values for basophils plotted in Figure 1 (based on routine white blood cell counts and differential counts) show only an occasional value above the normal range and even the highest values are not striking in comparison with the values observed by Moloney and Lange[9] in cases of early leukemia in atomic bomb survivors.

The persistent lymphopenia subsequent to March, 1952, the occasional appearance of immature granulocytes in small numbers, and the appearance of nucleated red blood cells, all antedating the appearance of blast cells in the peripheral blood (Fig. 1), are very similar to the findings of Moloney and Lange in cases of early myelogenous leukemia in atomic bomb survivors noted above. However, these hematologic similarities cannot justifiably be regarded as evidence for the etiologic role of radiation in the induction of leukemia in this particular case, especially in view of many points of similarity between this case and the cases of preleukemic acute human leukemia described by Block, Jacobson, and Bethard[1] in patients without previous notable radiation exposure. To our knowledge no one has described hematologic criteria which would make possible the differentiation of "spontaneous" from "radiation induced" leukemia even when observations over a long "preleukemic" period are available.

At least 9 other cases of leukemia complicating high dose I^{131} therapy for thyroid cancer have been described in the literature to date.[2,4,5,13,17] It is of considerable interest

that all 9 of these cases and the case reported herein have been of the acute variety. Although the pertinent published details are in some instances fragmentary, at least 4 of the 10 cases have presented at one time or another the picture of aleukemic leukemia. In the cases among Japanese survivors[11] and in the cases of spinal arthritis given roentgen ray treatment,[3] the acute form was similarly preponderant. In the latter series of 30 cases of the acute type, 20 presented in an aleukemic phase.

SUMMARY

The clinical, hematologic, and pathologic findings of a patient with thyroid cancer who developed leukemia following radioactive iodine therapy are presented. With respect to iodine metabolism, the tumor was highly functional and histologically was well differentiated. The metastatic deposits were primarily skeletal. Acute myelogenous leukemia of the "aleukemic" variety developed after the patient had received a total of 805 mc of I^{131} therapeutically over a 4 year period. The total radiation dose to the blood was estimated to be 1,600 rads. The total biologically effective radiation dose to the bone marrow was estimated to be about 44 per cent of the radiation dose to the blood. Those clinical and hematologic features of the case consonant with a radiation etiology of the leukemia are discussed and reference is made to 9 additional cases from the literature in which leukemia complicating radioactive iodine therapy of thyroid cancer has been described.

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SOME OBSERVATIONS ON RADIATION DOSE TO BONE MARROW DURING I^{131} THERAPY OF THYROID CANCER*

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THE purpose of this paper is to record the dose data for a case of leukemia complicating I^{131} therapy[9] and to present evidence that the biologically effective bone marrow dose is substantially less than the blood dose during I^{131} therapy of thyroid cancer. Three factors contributing to the difference in blood and bone marrow dose are discussed.

METHODS AND THEORETIC CONSIDERATIONS

For radiation dose computation we have modified the equation of Berman, Rall and Heslin.[1] With additional terms to provide for beta absorption by bone trabeculae and inequality of blood and bone marrow concentrations of isotope, the modified equation in derivative form is

$$(1)\quad R_s(t) = cAe^{-\lambda t}\left[\bar{E}_\beta m_i(t) r(1-a) + \bar{E}_\gamma \frac{k_{is}}{V_s}(q_{i1}(t) + q_{i2}(t)) + \bar{E}_\gamma \frac{k_{Ts}}{V_s} q_T(t)\right].$$

Here $R_s(t)$ is the combined beta and gamma dose rate to the marrow at time t; c a conversion factor to appropriate energy units; A the administered dose in millicuries; λ the physical decay constant of I^{131}; $\bar{E}_\beta$, $\bar{E}_\gamma$ the average beta and gamma energy, respectively, of I^{131} per disintegration; r the ratio of I^{131} concentration in bone marrow to that in blood; a the fraction of beta energy released in marrow absorbed by bone trabeculae; k_{is}, k_{Ts} the fraction of gamma energy originating in the body iodine spaces and in tumor, respectively, which is absorbed by the marrow; $m_i(t)$, the fraction of administered I^{131} per cm.^{3} of blood as a function of time; $q_{i1}(t)$, $q_{i2}(t)$, $q_T(t)$ the fraction of administered I^{131} as a function of time in the body iodide space, body organic iodine space, and in tumor, respectively; V_s the volume in cm.^{3} of bone marrow.

The bracketed portion of equation (1) was evaluated from the patient's isotopic data and the result was resolved graphically to a sum of exponential terms

$$\sum_i D_i e^{-\alpha_i t}.$$

With a new set of coefficients X_i defined as $X_i = cAD_i$, the evaluated equation (1) was written in the form

$$(2)\qquad R_s(t) = \sum_i X_i e^{-(\alpha_i+\lambda)t}.$$

The accumulated marrow dose at time t, $S(t)$ and for large values of time, $S(\infty)$ was then obtained by integrating equation (2) analytically:

$$(3a)\qquad S(t) \equiv \int_0^t R_s(t)dt = \sum_i \frac{X_i}{\alpha_i+\lambda}\left[1 - e^{-(\alpha_i+\lambda)t}\right];$$

$$(3b)\qquad S(\infty) \equiv \int_0^\infty R_s(t)dt = \sum_i \frac{X_i}{\alpha_i+\lambda}.$$

To assess the role of biological recovery during radiation exposure we have used Davidson's[5] formulation of the Blair theory:

$$(4)\quad S_s(t_1) = f\int_0^{t_1} R_s(t)dt$$

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$$+ (1 - f) \int_0^{t_1} e^{-\beta(t_1 - t)} R_s(t) dt.$$

Here $S_e(t)$ denotes the biologically effective marrow dose at time t (the physical dose corrected for biological recovery), f the irreparable fraction of the radiation dose, and β the fractional recovery rate. Substituting equation (2) in equation (4), integrating, and changing t_1 to t gives

$$(5) \qquad S_e(t) = f \sum_i \frac{X_i}{\alpha_i + \lambda} [1 - e^{-(\alpha_i + \lambda)t}] + (1 - f) e^{-\beta t} \sum_i \frac{X_i}{\alpha_i + \lambda - \beta} [1 - e^{-(\alpha_i + \lambda - \beta)t}].$$

Insofar as gamma energy absorption is concerned, the widespread and more or less uniform body distributions of blood and bone marrow may be regarded as similar.[1] It follows, if in equation (1), r and (1-a) be equated to unity and the result carried through equations (1) to (5), that one obtains an analogous set of equations for radiation dose rate at time t, $R_B(t)$, accumulated dose at time t, $B(t)$, accumulated dose for large values of time, $B(\infty)$, and biologically effective dose at time t, $B_e(t)$, for blood, respectively.

The data available for analysis are presented in Figure 1. Of the functions required to evaluate equation (1) only $m_i(t)$ was directly available from the data. The daily urine curve, $dq_u(t)/dt$, and the curve of cumulative urinary excretion, $q_u(t)$, were analyzed for the asymptotic value of cumulative urinary excretion, $q_u(\infty)$, as described elsewhere.[8] k_{ie}, the rate constant of renal iodide excretion, was estimated from ancillary tracer data by the method of Keating *et al.*[7] The other required functions were evaluated from the blood and urine data by applying the following equations, which are consonant with known quantitative features of iodine metabolism.[12]

$$(6) \qquad q_{i1}(t) = \frac{dq_u(t)}{dt} \cdot \frac{1}{k_{ie}} \text{ (Ref. 8)}$$

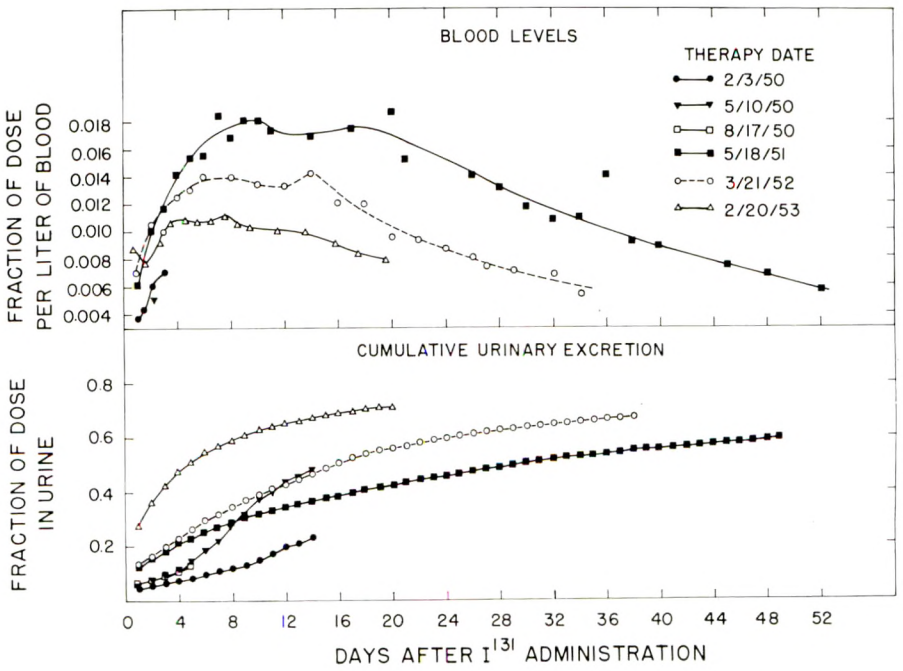


Fig. 1. Isotopic data for the 6 therapies. Available data were confined to assays of whole blood and urine.

$$(7) \quad m_{i1}(t) = q_{i1}(t)/V_{i1}$$

$$(8) \quad q_{i2}(t) = V_{i2}[m_i(t) - m_{i1}(t)] \text{(Ref. 1)}$$

$$(9) \quad q_F(\infty) = 1 - q_u(\infty)$$

$$(10) \quad k_{BF} = q_F(\infty) \Big/ \int_0^\infty q_{i2}(t)dt$$

$$(11) \quad q_F(t) = k_{BF} \int_0^t q_{i2}(t)dt$$

$$(12) \quad q_T(t) = 1 - q_{i1}(t) - q_{i2}(t) - q_u(t) - q_F(t).$$

Here $m_{i1}(t)$ is the fraction at time t of administered I^{131} per cm.^{3} of body iodide space; V_{i1}, V_{i2} the volume of the body iodide space and the body organic iodine space, respectively, relative to their concentration in the whole blood; $q_F(t)$, $q_F(\infty)$ the cumulative fraction of administered I^{131} in feces at time t and at infinite time, respectively; k_{BF} the rate constant of fecal excretion of organic iodine.

Values for constants taken from the literature or derived from the patient data are included in Table 1. V_{i1} and V_{i2} were computed from literature values for iodide and thyroxine partition between erythrocytes and plasma and their volumes of distribution relative to plasma concentration and body weight.[2,6,12] V_T, the tumor volume, was estimated from diameters of the lesions on pelvic roentgenograms. k_{TT}, k_{Tb}, and k_{bb}, the fraction of gamma energy originating in tumor absorbed by tumor, the fraction originating in tumor absorbed by the entire body, and the fraction originating in the body iodine spaces absorbed by the body, respectively, were estimated from the tables and formulae of Bush[3,4] as the ratio of the appropriate integral dose rate to the integral dose rate from the same quantity of gamma emitter to an infinite water absorber. The required constants

TABLE I

RADIATION DOSE ESTIMATES FOR BLOOD, DATA PARAMETERS, AND VALUES FOR PERTINENT CONSTANTS

Therapy No.	1	2	3	4	5	6	Total
Treatment Date	2/3/50	5/10/50	8/17/50	5/18/51	3/21/52	2/20/53	
A (millicuries)	50	50	200	182	168	155	805
$q_u(\infty)$ (fraction of dose)				0.66	0.73	0.75	
$q_F(\infty)$ (fraction of dose)				0.34	0.27	0.25	
k_{BF} (fraction per day)				0.041	0.053	0.061	
V_{i1} (cm.^{3})				19,400	19,900	18,300	
V_{i2} (cm.^{3})				10,500	10,900	10,000	
$B(\infty)$ (rads)	122*	109*	426*	410	300	230	1,600
$\int_0^{14}[1-q_u(t)]\,e^{-\lambda t}dt$ (days)	7.34	6.54		6.33	6.00	4.32	
$\int_0^{5}[1-q_u(t)]\,e^{-\lambda t}dt$ (days)			3.70	3.47	3.40	2.68	
$B(\infty)/A\int_0^{14}[1-q_u(t)]\,e^{-\lambda t}dt$ (rads mc^{-1} days^{-1})				0.356	0.298	0.344	
$B(\infty)/A\int_0^{5}[1-q_u(t)]\,e^{-\lambda t}dt$ (rads mc^{-1} days^{-1})				0.649	0.525	0.553	

Mean body weight: 50 kg.
Body height: 160 cm.
$\overline{E}_\beta$ 0.195 mev. (Ref. 1)
$\overline{E}_\gamma$ 0.397 mev. (Ref. 1)
λ 0.0854 days^{-1} (Ref. 1)
V_T 940 cm.^{3}
V_b 5×10^4 cm.^{3}
k_{ie} 1.54 days^{-1}
c 5.12×10^4 rads days^{-1} mev.$^{-1}$ mc^{-1} (Ref. 1)
k_{bb} 0.26
k_{TT} 0.095
k_{Tb} 0.30
k_{is}/V_s 5.2×10^{-6} cm.$^{-3}$
k_{Ts}/V_s 4.3×10^{-6} cm.$^{-3}$

* See text for method of estimation.

were then obtained from the relations:

$$\frac{k_{is}}{V_s} = \frac{k_{bb}}{V_b}; \qquad \frac{k_{Ts}}{V_s} = \frac{k_{Tb} - k_{TT}}{V_b - V_T} \text{ (Ref. 1)}$$

RESULTS AND DISCUSSION

The therapy number and treatment dates for our patient are given in Table 1. For therapies 4–6, values for the blood dose, $B(\infty)$, obtained by evaluating equations (1) and (3b) (equating r and 1-a to unity) are presented; for therapies 1–3, brevity of data collection periods prevented evaluation of the dosimetry equations. $B(\infty)$ for therapies 1–3 was approximated as follows:

From therapies 4–6, the mean value of the ratio

$$B(\infty)/A\int_0^t [1 - q_u(t)]e^{-\lambda t}dt$$

was extrapolated to therapies 1–3, choosing t to coincide with the shorter urine collection periods. The maximal spread of 24 per cent in ratio values entering the mean value extrapolated provides some justification for the procedure (Table 1).

$B(\infty)$ has been found to correlate well with the degree of hematopoietic depression and to serve as a useful guide in I^{131} therapy.[11,15] A satisfactory estimate of the maximal biologically effective bone marrow dose in isotope therapy would ideally have the added advantage of permitting comparison of certain dose response relations with those of subjects exposed to short duration whole body irradiation. Accordingly, the hematologic response of our patient[9] (see Fig. 1) to therapies 3–5, the three largest, for which the mean blood dose was 379 rads (Table 1) was compared to blood changes of 4 patients given short duration total body irradiation[10] in a carefully measured average total body dose of 130 rads.[14] The hematopoietic depression of our patient, judged by minimum values for neutrophils, lymphocytes, and platelets, was somewhat less than that of the patients given total body irradiation. This discrepancy of roughly a factor of three in radiation dose associated with comparable degrees of hematopoietic depression suggests that the uncorrected blood dose in I^{131} therapy may markedly exceed the biologically effective marrow dose.

For therapies 4–6 evaluation of equation (1) in its original form[1] indicated the following average percentage contributions to $B(\infty)$ from various sources: from beta energy originating in blood, 69 per cent; from gamma energy originating in tumor, 23 per cent; from gamma energy originating in body iodine spaces, 8.3 per cent. Now evaluation of the beta contribution involves only the blood curve [see equation(1)] and in no way depends on the validity of equations (6) to (12) or of constants for gamma energy absorption. Accordingly, even if one discounts entirely the gamma contribution because of its greater uncertainty, $B(\infty)$ becomes $0.69(379) = 262$ rads and the above noted discrepancy remains.

Three factors were examined in an attempt to resolve the discrepancy. (1) A literature search revealed little data from which r, the bone marrow:blood I^{131} concentration ratio could be estimated. The necropsy data of Trunnel *et al.*[16] for 4 cases given I^{131} 2–21 days before death gave a mean value for r of 0.62. (2) From histologic studies Robertson and Godwin[13] estimated that the trabeculae of cancellous bone absorb a fraction, a, of I^{131} beta energy liberated in marrow equivalent to 0.21. (3) For man, Davidson[5] has proposed a value for β, the fractional rate of biological recovery from radiation, of 0.024 per day and a value for f, the irreparable fraction of the radiation dose, of 0.10.

Equations (1) to (5) were evaluated for bone marrow and the analogous set of equations for blood for therapies 4–6 using the above values for r, a, β, and f. The average value obtained for $S(\infty)/B(\infty)$ was 0.65. This indicates that beta absorption by bone trabeculae and the inequality of blood and bone marrow concentrations of I^{131} to the extent indicated by literature data can significantly reduce the physical dose to bone marrow relative to that of

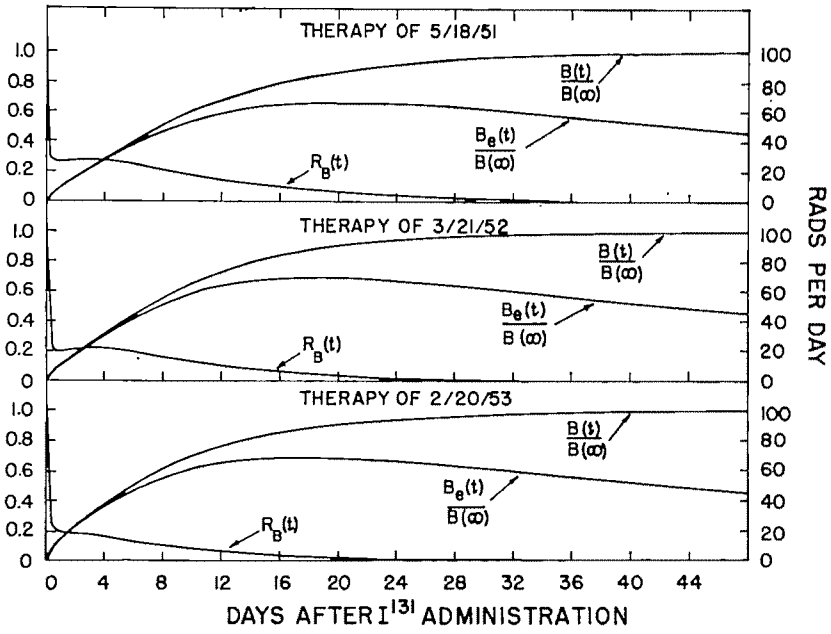


FIG. 2. Plots of three evaluated dose functions for the last 3 therapies. $R_B(t)$ is plotted with respect to the right ordinate, the other two functions with respect to the left. See text for definition of symbols.

blood. The evaluated dose functions for blood plotted in Figure 2 emphasize the importance of biological recovery during the protracted exposure, subject to the uncertainty in the values for β and f. Maximal values for $B_s(t)/B(\infty)$ are reached at 18 to 22 days and range from 0.67 to 0.69. Similar plots of $S_s(t)/B(\infty)$ gave maximal values ranging from 0.43 to 0.45 with a mean of 0.44. If these results are extended to therapies 3–5, the average maximal biologically effective bone marrow dose is estimated to be approximately 0.44 of the mean blood dose or $0.44(379) = 167$ rads. This is not far removed from the mean dose of 130 rads absorbed by the patients of Miller *et al.*[10] who were given whole body x-irradiation and who showed a comparable but somewhat more pronounced hematologic response.

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THE SUCCESSIVE CHANGES IN THE SKIN EPITHELIUM OF THE YOUNG AXOLOTL (SIREDON MEXICANUM) AFTER ROENTGEN IRRADIATION*

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IT HAS long been established that changes in the skin epithelium are very important for the evaluation of irradiation effects,[4] but knowledge of successive changes in this tissue after irradiation is very limited.

Investigation of the effect of local irradiation on the development of extremities of the young axolotl[6] showed the picture of changes in the developmental process rather than the peculiarity of successive changes of this particular tissue. The information in this paper is incomplete because the larger doses of irradiation (6,000 r and 9,000 r) were not used. The results of the investigation of the effect of local irradiation on the development of the tail of young axolotl[5] are incomplete because only two periods of fixation (35–40 days and 85–100 days after treatment) were described.

In the papers concerning the lethal effects of irradiation on young axolotl,[11] the formation of giant cell epithelium in typical form was described in 17 animals fixed between 21 and 30 days after irradiation with 3,000 r and 6,000 r. But the exact picture of successive changes in the treated epithelium even after irradiation with these doses is not known. The effect of the smaller and larger doses was not investigated completely.

The appearance of normal skin epithelium varies according to the age of the animal and the location of the tissue (Fig. 1–6). The thickness of the epithelium in one animal can be twice that of another animal of the same age. This great variation was observed especially in very young animals; for example, in animals 14 days after hatching—the day of irradiation of experimental animals (Fig. 1–2). The cells of the epithelium of very young animals can be a little larger than the cells of epithelium of animals about 3 months old (compare Fig. 2 and 6). A typical finding for young epithelium is the complete absence of Leydig's cells (Fig. 1, 2 and 4) and the comparative rarity and the small size of intraepithelial pigment cells (melanophores). The thickness of the epithelium and the number of cell layers increase greatly with age (Fig. 1 and 6), but the surface of the epithelium is always even and separation of cells or cell complexes is not observed.

MATERIALS AND METHODS

For this investigation 127 animals from one spawning were irradiated 14 days after hatching with 9,000 r, 6,000 r, 3,000 r,

All photomicrographs made under the same magnification (510×).

FIG. 1 and 2. Epithelium of two different animals 14 days after hatching. On this day, the heads were irradiated in experimental animals. (C. T.) Cells of loose connective tissue; (E) skin epithelium; (P) under epithelial pigment cells (melanophores). FIG. 3. Epithelium of animal 59 days after hatching. (C. T.) Cells of loose connective tissue; (E) cells of skin epithelium; (L. C.) Leydig's cells. FIG. 4. Epithelium of animal 28 days after hatching. (C. T.) Cells of loose connective tissue; (E) skin epithelium. FIG. 5. Epithelium of animal 65 days after hatching. (E) Cells of skin epithelium; (L. C.) Leydig's cells; (P) under epithelial pigment cells (melanophores). FIG. 6. Epithelium of animal 94 days after hatching. (E) Cells of skin epithelium; (L. C.) Leydig's cells; (P) intraepithelial melanophore.

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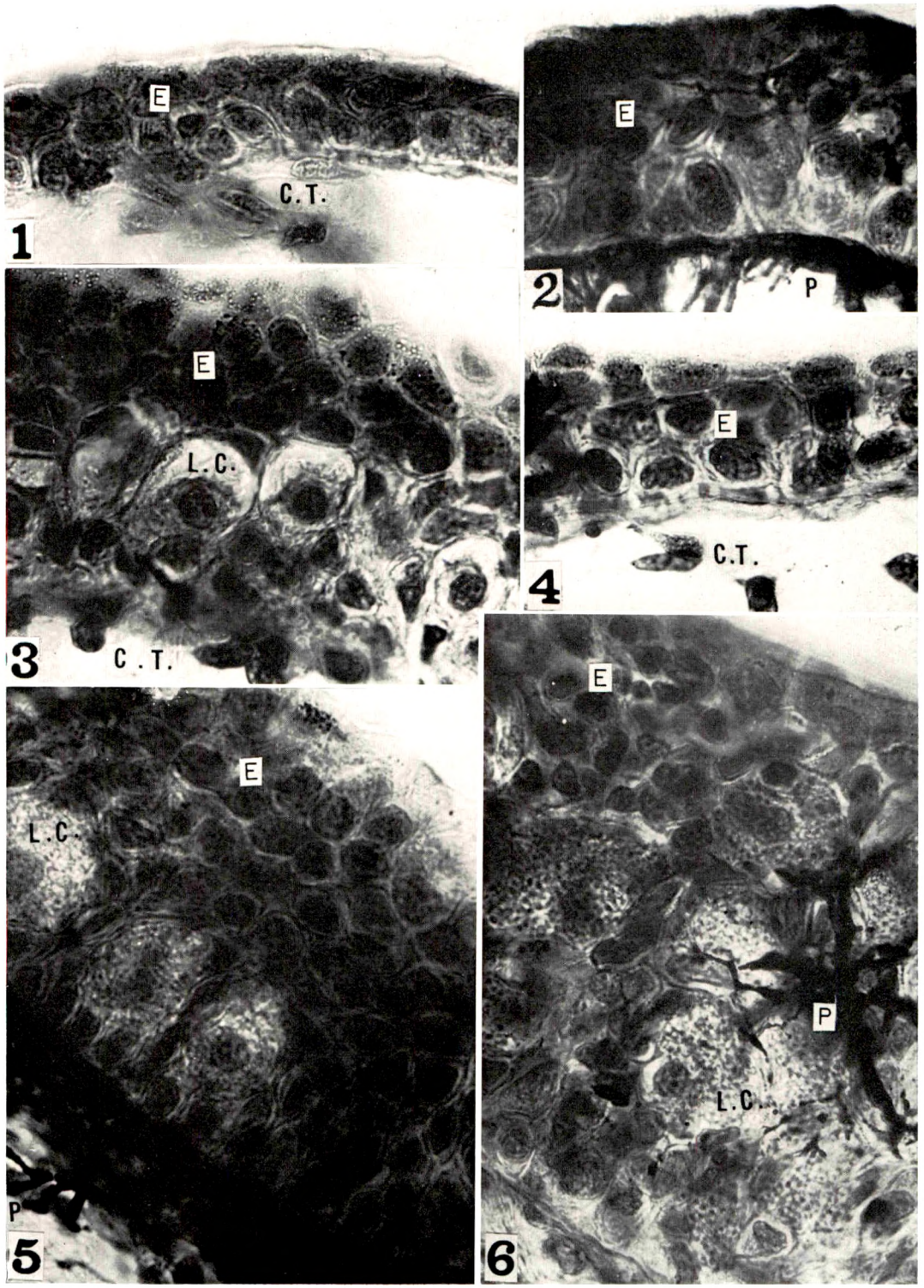


Plate 1. *Normal development of the skin epithelium of young control animals.*

1,000 r, 500 r and 250 r and 20 animals served as untreated controls.

Irradiation conditions were: 100 kv., 5 ma., 0.25 mm. Al filter, beryllium window tube; half value layer 0.55 mm. Al; intensity 436 r/min. in air; target to object distance 13 cm. During irradiation the animals were anesthetized by means of weak aqueous solution of tricaine methanesulfonate (MS222); they were placed on a piece of cardboard covered with wax paper and several layers of moistened filter paper. Only the heads were irradiated, the non-irradiated portions were shielded with a lead covering (made from a 4 mm. lead sheet) with a round radiation localizer 6.5 cm. in diameter.[7] The animals were arranged in radial positions within a circle during irradiation. Immediately after treatment, the animals were put into water, where they recovered from the anesthesia. After irradiation with 9,000 r, one animal was sacrificed and fixed every day. After irradiation with all other doses, 2 animals were sacrificed and fixed every week. All the animals which were dying were also fixed before they died.

For histologic study, animals were fixed in acetic mercuric chloride formalin (Stieve[51]). The material was embedded in paraffin with 5 per cent bees wax and sectioned at 8 μ. The sections were stained with Ehrlich's hematoxylin and eosin and in almost all cases photomicrographs were made with the same magnification (×510). Only in rare cases photomicrographs were made under lower magnification (×100).

RESULTS

THE EFFECTS OF IRRADIATION WITH 250 r

We did not observe any definite changes in the epithelium of the skin after irradiation of the head of young axolotl with 250 r. It is possible that this effect is very small or only temporary and soon disappeared and therefore was not shown in our material after weekly fixation.

THE EFFECTS OF IRRADIATION WITH 500 r

The effects of this dose are very definite with perhaps the most interesting results. The epithelium of the skin 7, 14 and 21 days after irradiation was normal in appearance and did not show any definite pathologic changes (Fig. 7, 8 and 9). Some cells of the epithelium 25 days after irradiation might have been slightly enlarged (Fig. 10), but this is questionable. Some portions of epithelium 28 days after irradiation (Fig. 11) were normal in appearance, but others (Fig. 12) showed a very definite pathologic change in the formation of giant cells, some of which had a quantity of pigment granules. The pathologic effect of radiation was more definite 35 days after irradiation (Fig. 13, 14, 15, 16, 17, 18, 19 and 21). For this period the typical findings were: formation of giant cells of maximal size (Fig. 13, 16, 17 and 19); formation of large and small vacuoles in the cytoplasm of the giant cells (Fig. 13, 14 and 17); an extremely uneven outer surface of the epithelium (Fig. 13, 14, 15, 16, 17, 18 and 21); protrusion of separate giant cells from

»»»→

All photomicrographs made with the same magnification (510×).

Fig. 7. Epithelium of animal 7 days after irradiation and 21 days after hatching. (C. T.) Cells of loose connective tissue; (E) skin epithelium. Fig. 8. Epithelium of animal 14 days after irradiation and 28 days after hatching. (E) Skin epithelium; (P) melanophores. Fig. 9. Epithelium of animal 21 days after irradiation and 35 days after hatching. (E) Skin epithelium; (P) under epithelial malanophore. Fig. 10. Epithelium of animal 25 days after irradiation and 39 days after hatching. (E) Cells of skin epithelium; (P) intraepithelial melanophore. Fig. 11. Epithelium of animal 28 days after irradiation and 42 days after hatching. (C. T.) Cells of loose connective tissue; (E) skin epithelium. Fig. 12. Epithelium of animal 28 days after irradiation and 42 days after hatching. (E) Enlarged cells of epithelium; (G) giant cells of epithelium with (P. G.) pigment granules; and (P) melanophores. Fig. 13. Epithelium of animal 35 days after irradiation and 49 days after hatching. (G) Giant cells of skin epithelium with large (V) vacuoles; or with accumulation of (VS) small vacuoles in cytoplasm.

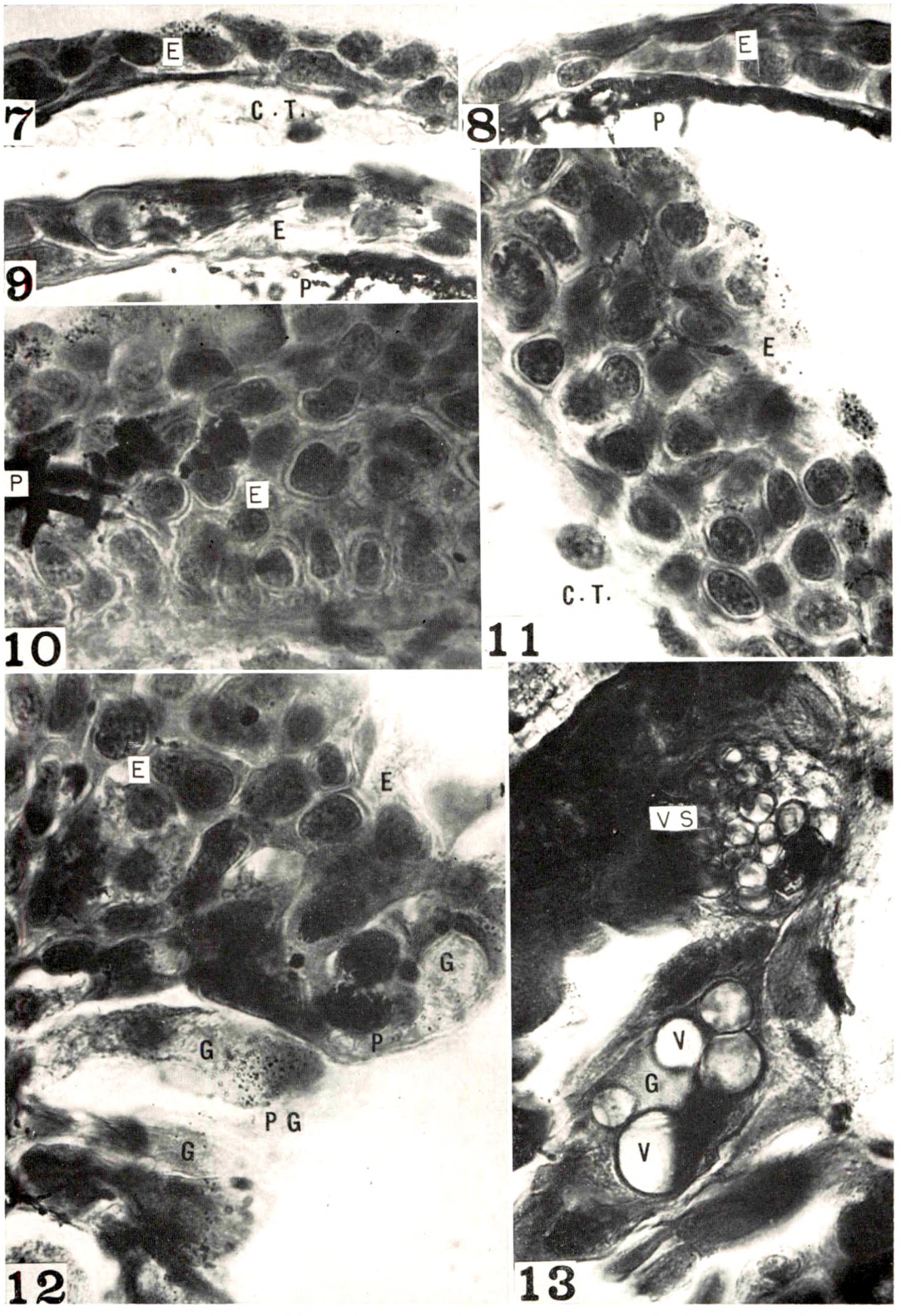


Plate II. *Successive changes in the skin epithelium after irradiation with 500 r.*

the outer surface of the epithelium (Fig. 14, 15, 16, 17 and 18); formation of deep cracks and spaces between the epithelial cells (Fig. 12, 13, 14, 15 and 21); and complete separation of some giant cells or cell complexes (Fig. 12 and 14).

The formation of giant cells was observed in some limited regions of skin epithelium side by side with normal or almost normal epithelium (Fig. 12, 14 and 17). In some cases the formation of large and narrow outgrowths was observed consisting mostly of giant cells (Fig. 14) with many pigment cells.

In some instances the giant cell epithelium had intraepithelial melanophores of large size (Fig. 14 and 16). In many giant epithelial cells, the accumulation of pigment granules in the cytoplasm was observed (Fig. 12, 14, 15 and 21). It is possible that these granules are the results of the destruction of melanophores. Many giant cells had several nuclei (two, three or more) (Fig. 19 and 21).

The giant cells of the degenerating epithelium gradually fell off and were replaced with normal epithelium. Such epithelium can be observed one week after irradiation and later (42 and 49 days after irradiation) (Fig. 20 and 22). It is interesting to compare the size of the giant cells (Fig. 19) and the cells of the normal epithelium which replaced the giant cell epithelium (Fig. 22). It is obvious that the giant cells are 6 to 7 times larger than the normal epithelial cell.

The effects of irradiation with 1,000 r

After irradiation with this dose, the nuclei of some epithelial cells became enlarged as soon as 7 days after irradiation (Fig. 23). Obviously, this can be explained by individual variation or individual sensitivity to irradiation. Usually, the size of the nuclei was almost the same at 14 days after irradiation (Fig. 24). Twenty-one days after irradiation, more definite signs of radiation effect could be noted (Fig. 25). The cells of the epithelium were greatly enlarged. Some of them had several nuclei. Giant cell degeneration of epithelium was observed 28 days after irradiation (Fig. 26 and 27). Many intraepithelial melanophores could be noted. The thickness of the epithelium differed in various instances; in some it was much thicker than normal (Fig. 26), in others it was very flat and consisted of giant cells disposed in one layer (Fig. 27). The degeneration and destruction of giant cell epithelium continued 35 days after irradiation (Fig. 28 and 29). Separate giant cells or cell complexes fell off (Fig. 28 and 29). Some multinucleated cells were noted (Fig. 29). Later (42 days after irradiation) the epithelium was replaced by normal epithelium (Fig. 30), which was also observed 56 days after irradiation (Fig. 31). The large number of Leydig's cell is typical for normal epithelium at this age.

The effects of irradiation with 3,000 r

The appearance of epithelium 7 days after irradiation with 3,000 r was normal (Fig. 32). This corroborates our conclusion that the enlarged nuclei which were observed 7 days after irradiation with 1,000 r were only individual variations. The epithelium 14 days after irradiation was still normal (Fig. 33), but 17 days after irradiation, only 3 days later, definitely abnormal patterns were observed (Fig. 34). The cells were greatly enlarged with many pigment granules. The epithelium 21 days after irradiation consisted only of one layer of enlarged cells (Fig. 35), but an animal fixed one day later (22 days after irradiation)

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All photomicrographs made with the same magnification (510×).

Fig. 14–16. Various portions of epithelium of different animals 35 days after irradiation and 49 days after hatching. (E) Cells of skin epithelium, normal or almost normal in size; (E. O.) epithelial outgrowth consisted mostly of (G) giant cells; (I. G.) isolated giant cells; (P) melanophores and processes of these cells; (P. G.) pigment granules; (V) great vacuoles in cytoplasm of giant epithelial cells.

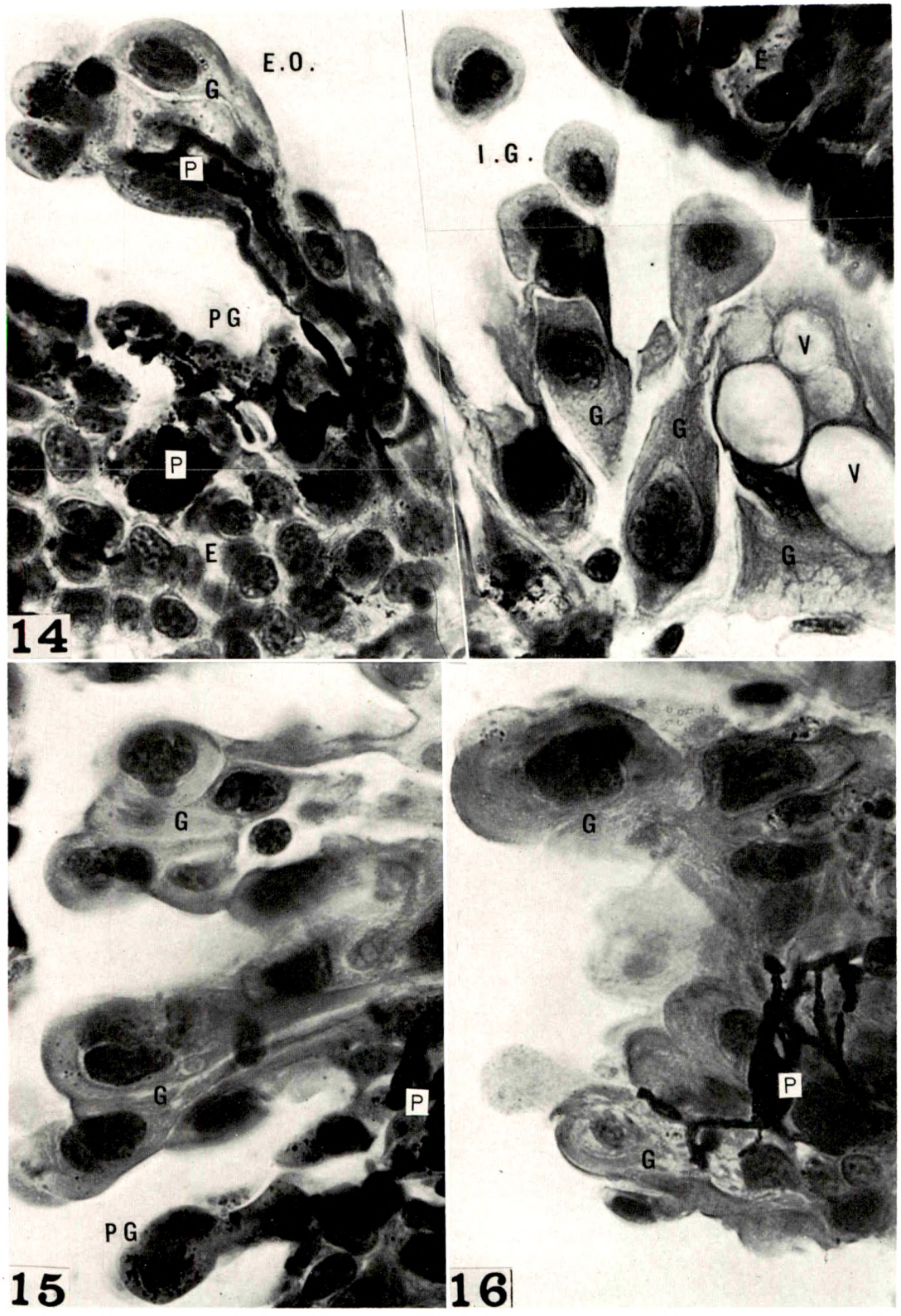


Plate iii. *Successive changes in the skin epithelium after irradiation with 500 r.*

had an epithelium containing typical giant cells (Fig. 38, 39 and 40). All the characteristic features which were described previously were also noted in this epithelium. In some cases the size of the nuclei of the giant cells was exceptionally large (Fig. 38). The formation of vacuoles (Fig. 38), an uneven outer surface (Fig. 38, 39 and 40), the protrusion of separate giant cells (Fig. 38 and 39), the formation of deep cracks between the cells and complete separation of some cells (Fig. 40) were also observed after irradiation with this dose. The protrusion of many separate giant cells which were noted after irradiation with 500 r (Fig. 18) was clearly observed after irradiation with this dose. Large giant cells were connected with the basal epithelium by a narrow pedicle (Fig. 39).

In animals fixed 28 days after irradiation, we were able to find only one layer of cells which were either enlarged (Fig. 36) or normal (Fig. 37); in some there were accumulations of pigment granules. It is however, necessary to consider this condition as an individual variation in reaction to irradiation. Probably, in most cases epithelium consisting of degenerating giant cells continues to exist much longer. In other cases we were able to observe such degenerate epithelium 35 days after irradiation (Fig. 41, 42 and 43). Some of these giant cells were almost completely separated from the basal epithelium (Fig. 41). Many of these cells had large amounts of pigment granules in the cytoplasm (Fig. 41 and 42). The epithelium of an animal fixed 50 days after irradiation was completely normal in appearance (Fig. 44).

The effects of irradiation with 6,000 r

The epithelium of animals 7 and 14 days after irradiation with 6,000 r was normal in appearance (Fig. 45 and 46); however, some portions of the epithelium fixed 14 days after irradiation were abnormal. The cells were definitely enlarged (Fig. 48). The same phenomenon was more evident 18 days after irradiation (Fig. 47).

The formation of epithelium consisting of degenerating giant cells was observed 23, 24 and 28 days after irradiation (Fig. 49, 50, 52, 53, 54, 55, 56 and 57), and protrusion of separate giant cells was definitely observed in almost all cases (Fig. 49, 50, 52, 53, 54, 56 and 57). The development of melanophores in large numbers, especially in the basal layers of the epithelium cells and under the epithelium, was typical (Fig. 49, 50 and 56), but in some cases large intracellular melanophores developed in giant cells (Fig. 50 and 56). Pigment granules accumulated in many giant cells, especially on their outer parts (Fig. 50, 51, 55 and 56). In comparison with control animals Leydig's cells could be found at this time only rarely (Fig. 49, 50 and 54). In many cases after irradiation with this dose, almost all the cells of the epithelium were transformed into giant cells (Fig. 53, 54 and 57).

In typical cases all the epithelium repre-

One photomicrograph (17) made with small magnification (100×), all others with large magnification (510×).

Fig. 17. General picture of distal end of lower jaw with typical modification of skin and oral epithelium of animal 35 days after irradiation and 49 days after hatching. (B) Bone; (C) cartilage; (C. T.) loose connective tissue; (E) epithelium of the skin consisting of giant and normal epithelial cells; (G) giant epithelial cell of maximal size; (V) great vacuole in cytoplasm of giant cell. Fig. 18. Epithelium of animal 35 days after irradiation and 49 days after hatching. (C. T.) Loose connective tissue; (G) giant cells of the epithelium. Fig. 19. Part of the section shown of Figure 17, with large magnification. (G) Giant cell with three nuclei. Fig. 20. Epithelium of animal 42 days after irradiation and 56 days after hatching, normal in appearance. (E) Epithelial cells; (L. C.) Leydig's cells. Fig. 21. Epithelium of animal 35 days after irradiation and 49 days after hatching. (G) Giant cells; (N) giant cells with four nuclei; (P. G.) pigment granules. Fig. 22. Epithelium of animal 49 days after irradiation and 63 days after hatching, normal in appearance. (E) Epithelial cells; (P) melanophores and their processes.

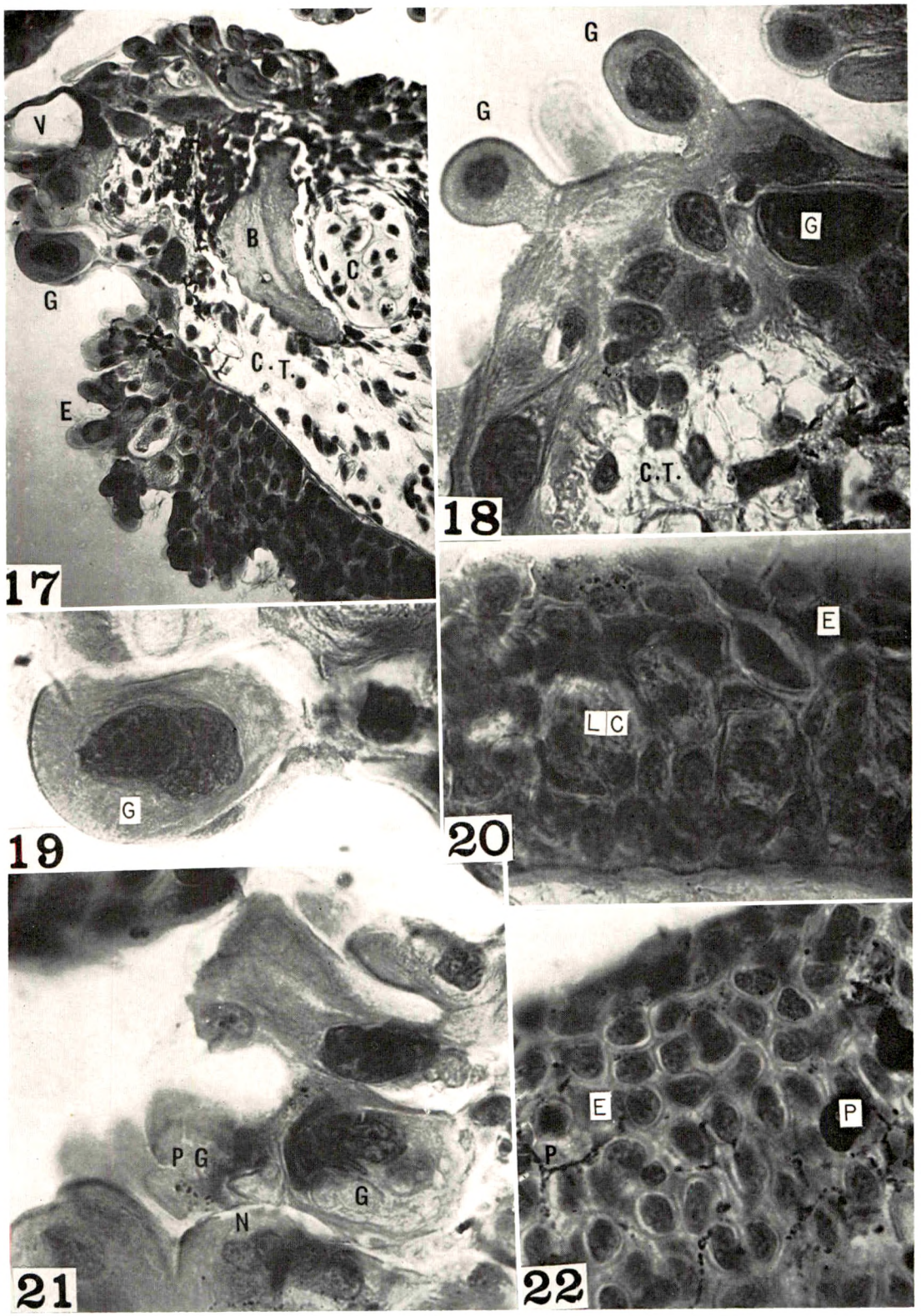


Plate iv. *Successive changes in the skin epithelium after irradiation with 500 r.*

sented one layer of giant cells which were connected only with the basal subepithelial tissue, but not with each other (Fig. 53). In some places the outer layer of giant cells was connected with one or two basal layers of giant cells (Fig. 54 and 57). In some instances the basal layer consisted of epithelial cells which were normal in size (Fig. 52) or of many layers of enlarged cells with many spaces between the cells (Fig. 51). In rare cases the outer giant cells were connected with the basal layers of epithelium containing many Leydig's cells (Fig. 50). On the last day of fixation, 28 days after irradiation (Fig. 57), the final degeneration of the treated epithelium was obvious, but replacement of such epithelium with normal epithelium, after irradiation with this dose, was not observed.

THE EFFECTS OF IRRADIATION WITH 9,000 r

After irradiation with 9,000 r normal epithelium was observed for only 2 days following irradiation (Fig. 58). In animals fixed 4 days after irradiation in some portions of the head the epithelium was normal in appearance (Fig. 59), but in other parts of the same head, the epithelial cells were slightly enlarged (Fig. 60). In the animals fixed 8 and 9 days after irradiation, the epithelial cells were definitely enlarged (Fig. 61, 62 and 63). In the cytoplasm of some epithelial cells, an accumulation of pigment granules was observed (Fig. 63 and 64). In animals fixed 10 days after irradiation, some portions of the epithelium consisted of cells of normal size, but the epithelium had a very uneven outer surface (Fig. 65), which is typical of degeneration. Another portion of the epithelium of the same animal (Fig. 66) consisted of enlarged cells and giant cells. Leydig's cells and large intraepithelial melanophores could be noted (Fig. 66).

In some animals fixed 10 days and 15 days after irradiation, the epithelium consisted only of giant cells (Fig. 64 and 67), but such giant cell degeneration which was observed after irradiation with small doses (especially with 3,000 r and 6,000 r) was not observed after irradiation with this dose. Only in rare cases was protrusion of separate giant cells observed (Fig. 67). Vacuoles of the cytoplasm and deep cracks and spaces between the cells were not observed. Many subepithelial and intraepithelial melanophores were observed in this epithelium (Fig. 67). In some cells great amounts of pigment granules accumulated (Fig. 64). Isolated Leydig's cells could be noted (Fig. 67). In animals fixed 17 days after irradiation (Fig. 68 and 70), some portions of the epithelium consisted of one layer of enlarged cells (Fig. 68) while other portions consisted mostly of giant cells with many melanophores (Fig. 70). In the last surviving animal (18 days after irradiation), the epithelium consisted of enlarged and giant cells with intracellular melanophores (Fig. 69). Replacement of such epithelium with normal epithelium after irradiation with this dose was not observed.

All photomicrographs made with the same magnification (510×).

Fig. 23. Epithelium of animal 7 days after irradiation and 21 days after hatching. (E) Enlarged cells of epithelium; (P) intraepithelial melanophore. Fig. 24. Epithelium of animal 14 days after irradiation and 28 days after hatching. (C. T.) Cells of loose connective tissue; (E) enlarged cells of epithelium. Fig. 25. Epithelium of animal 21 days after irradiation and 35 days after hatching. (C. T.) Cells of loose connective tissue; (E) cells of epithelium greatly enlarged; (N) cell of epithelium with three nuclei. Fig. 26 and 27. Epithelium of various animals 28 days after irradiation and 42 days after hatching. (C. T.) Cells of loose connective tissue; (G) giant cells of epithelium; (P) melanophores. Fig. 28 and 29. Epithelium of animal 35 days after irradiation and 49 days after hatching. Destruction of (G) giant cell epithelium. (C. T.) Cells of loose connective tissue; (I. G.) isolated giant cells; (G. N.) almost isolated giant cell with three nuclei; (GR) pigment granules in cytoplasm of giant cells; (P) melanophore.

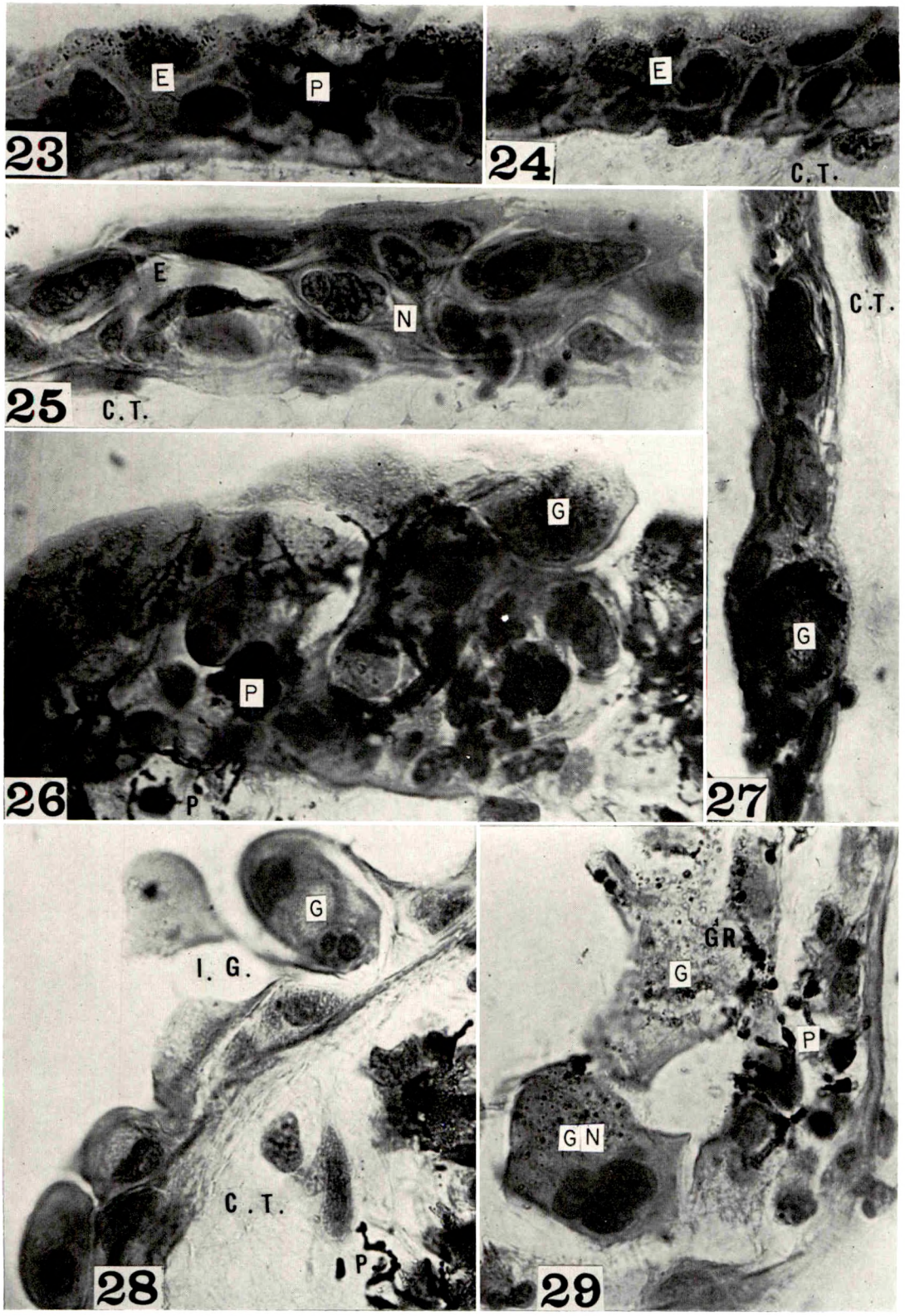


Plate v. *Successive changes in the skin epithelium after irradiation with 1,000 r.*

DISCUSSION

A comparison of latent periods after irradiation with different doses shows that the first positive pathologic changes in the skin epithelium can be observed 28 days after irradiation with 500 r; 21 days after irradiation with 1,000 r; 17 days after irradiation with 3,000 r; 14 days after irradiation with 6,000 r; and only 4 days after irradiation with 9,000 r. After irradiation with 500 r and 1,000 r, the animals lived 70 days; after irradiation with 3,000 r, they lived 56 days; after irradiation with 6,000 r they lived 29 days and after irradiation with 9,000 r, only 18 days.

It has been described[15] that corneal epithelium after irradiation was gradually disorganized and disappeared completely. After this, corneal epithelium was replaced with normal skin epithelium with many Leydig's cells, if the animal survived long enough. We did not observe this phenomenon after irradiation with larger doses (9,000 r and 6,000 r) because the animals died before the replacement occurred. This also applies to the skin epithelium. Replacement of degenerated skin epithelium with normal epithelium occurs 40 to 50 days after irradiation with medium doses (500–3,000 r). After large doses, the animals lived from 29 days (after irradiation with 6,000 r) to only 18 days (after irradiation with 9,000 r).

A comparison of the reaction of the skin and corneal epithelium to irradiation[15] showed that the skin epithelium has the same threshold of sensitivity as the corneal epithelium. A dose of 500 r has definite destructive effects on the skin epithelium while a dose of 250 r has no such effect. Therefore, we can conclude that the threshold of sensitivity of skin epithelium is between 250 r and 500 r.

The reaction of pigment cells (melanophores) in this material is unusual. We did not observe the reduction in the number of pigment cells and the formation of globular melanophores without processes, which were described previously in irradiated axolotl tails.[16] On the contrary, the melanophores under the epithelium (Fig. 26, 28, 30, 31, 35, 43, 44 and 56) and especially the intraepithelial melanophores (Fig. 10, 12, 14, 16, 26, 29, 34, 43, 47, 50, 51, 56, 62, 64, 66, 67, 69 and 70) were observed more often than on normal epithelium (Fig. 1–6). In some cases, the development of intraepithelial melanophores was especially great (Fig. 26, 34, 50, 56 and 66). The disappearance of the melanophore processes was not observed, and in some cases these processes were especially large and long (Fig. 14, 16, 56, 62 and 67). The accumulation of pigment granules in the cytoplasm of the epithelial cells, which was observed in normal epithelium only rarely and which is probably the result of degeneration and destruction of melanophores, was observed in very many cases after irradiation with different doses. (Fig. 12 14, 29, 41, 42, 55, 56, 63,

Fig. 30. Epithelium of animal 42 days after irradiation with 1,000 r and 56 days after hatching, normal in appearance. (E) Epithelial cells; (P) pigments cells—melanophores. Fig. 31. Epithelium of animal 56 days after irradiation with 1,000 r and 70 days after hatching. Epithelium is normal in appearance. The presence of large numbers of (L. C.) Leydig's cells is typical for epithelium of such age. (E) Epithelial cells; (P) melanophores. Fig. 32. Epithelium of animal 7 days after irradiation with 3,000 r and 21 days after hatching. (C. T.) Cells of loose connective tissue; (E) epithelial cells; (P) melanophores. Fig. 33. Epithelium of animal 14 days after irradiation with 3,000 r and 28 days after hatching. (E) Epithelial cells; (G. R.) pigment granules. Fig. 34. Epithelium of animal 17 days after irradiation with 3,000 r and 31 days after hatching. (E) Somewhat enlarged epithelial cells with pigment granules in cytoplasm; (P) melanophores. Fig. 35. Epithelium of animal 21 days after irradiation with 3,000 r and 35 days after hatching. (E) Epithelium consisting of one layer of enlarged cells; (P) melanophores. Fig. 36 and 37. Epithelium of various portions of head of animal 28 days after irradiation with 3,000 r and 42 days after hatching. (C. T.) Cells of loose connective tissue; (E) epithelial cell of normal size; (EN) epithelium consisting of one layer of cells. Some of these cells are enlarged, other have normal size; (P) epithelial cells with great accumulation of pigment granules.

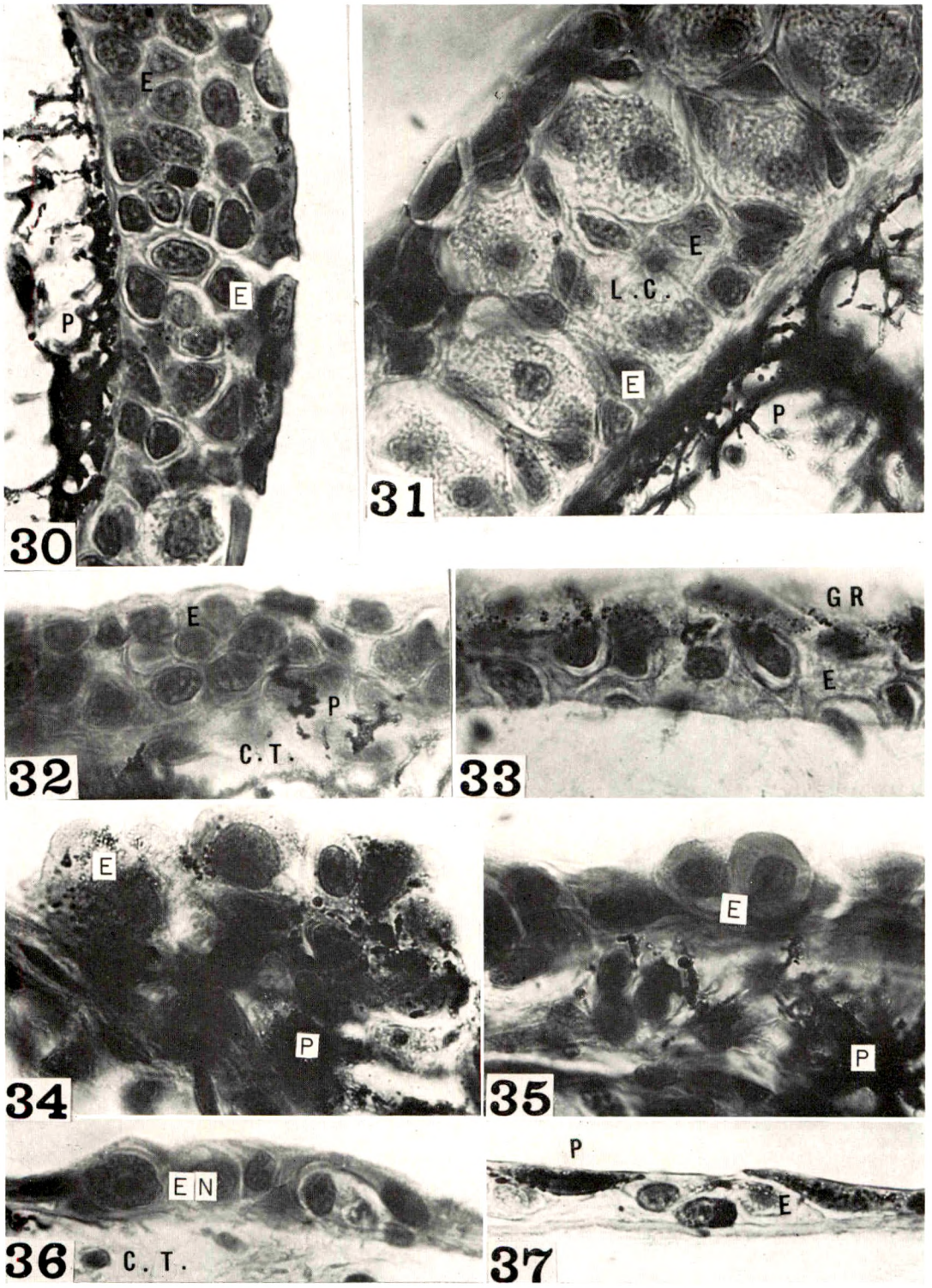


Plate vi. *Successive changes in the skin epithelium after irradiation with 1,000 r (Fig. 30 and 31) and 3,000 r (Fig. 32–37).* All photomicrographs made with the same magnification (510×).

66 and 67). In some cases the number of these granules was especially great (Fig. 42, 51, 64 and 70). In normal epithelium this was never observed.

It is interesting to compare the reaction of melanopores in the skin epithelium of the head with the development of melanophores in the epithelium of the cornea after irradiation.[15] The epithelium of the cornea normally has no melanophores but after irradiation with 500 r–9,000 r, the development of melanophores was observed in many cases. After irradiation with only 250 r, however, they did not develop. Pigment cells appear in irradiated corneal epithelium as large compact rounded cells, or as typical melanophores with many processes, or finally as an accumulation of many pigment granules. The progressive development of melanophores in new regions where they are normally nonexistent can be considered as an example of roentgen stimulation.

We have also observed in the epithelium of the skin phenomena which can be considered the result of roentgen stimulation. This is the formation of peculiar outgrowths, large and narrow, consisting mostly of giant cells (Fig. 14). We did not observe mitotic figures in these outgrowths, but this shows only that this formation does not continue to grow at the moment of fixation. To explain such formation only by the rearrangement or moving of the epithelial cells is difficult or perhaps impossible. This formation differs very much from the protrusion of separate giant cells from the outer surface of the epithelium (Fig. 14—from the right side, Fig. 15 and others). In the last cases the protrusion is probably the result of weakening of the connections between the cells of the epithelium. The final result is the complete separation of many giant epithelial cells (Fig. 14, 28 and 29). Contrarily, in the stimulated outgrowth (Fig. 14) we have observed many cells closely connected with one another. It is significant that many processes of the melanophores penetrated into this outgrowth (Fig. 14). This can be better explained by the active ingrowing of melanophore processes into the stimulated growing complex of cells than by the possible penetration of this process during the rearrangement of epithelial cells.

Our previous observations showed that different types of outgrowth can be formed as a result of local roentgen irradiation. Such stimulated development of epithelial cells was described in the tail regeneration of tadpoles of Pelobates fuscus[53] and in irradiated tails of Rana catesbiana tadpoles.[10] In the latter instance unusually large epithelial outgrowths were described in the shape of long strips or layers between portions of degenerating giant cell epithelium on the distal tail region. The cells of these outgrowths were normal in size. The development of these abnormal epithelial formations was definitely the result of intensive mitotic activity. Many mitotic figures were observed in some places in close proximity of the typical degenerating giant cell epithelium.

The problem of roentgen stimulation was discussed many times in previous publications.[8,12,13,15] Socurova[57] mentioned that there were about 45 reports describing the stimulation of various cell processes in microorganisms under the influence of ion-

All photomicrographs made with the same magnification (510×).

FIG. 38. Epithelium of animal 22 days after irradiation and 36 days after hatching. (G) Giant cells with an exceptionally large nucleus and vacuoles (V) in cytoplasm. FIG. 39 and 40. Epithelium of various animals 22 days after irradiation and 36 days after hatching. (G) Giant epithelial cells of different sizes; (I. C.) isolated giant cells. FIG. 41–43. Epithelium of various animals 35 days after irradiation and 49 days after hatching. (G) Giant epithelial cells with pigment granules; (I. G.) isolated giant cells; (P) melanophores; (P. G.) giant cell with an especially great accumulation of pigment granules. FIG. 44. Epithelium of animal 56 days after irradiation and 70 days after hatching is normal in appearance. (E) Epithelial cells; (L. C.) Leydig's cell; (P) melanophores.

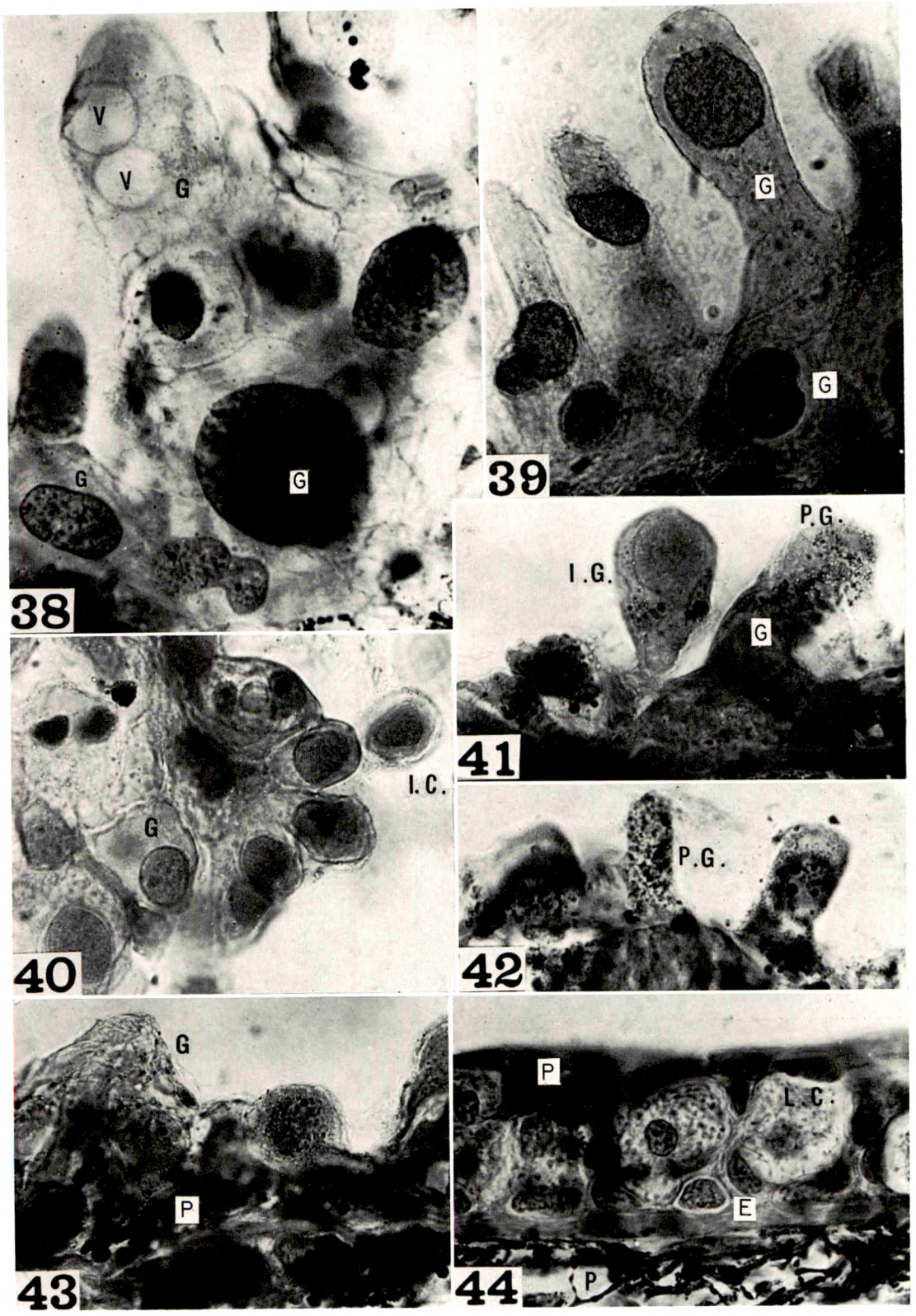


Plate vii. *Successive changes in the skin epithelium after irradiation with 3,000 r.*

izing radiation and recorded her own experiments with bacteria. Activation of the development of microorganisms under the influence of radiation amounts principally to acceleration of the rate of cell division, of accumulation of the bio-mass and of intensification of other physiologic processes. According to James and Muller,[30] a significant increase in the rate of mitosis was found after treatment of yeast Saccharomyces cerevisiae with 500 r of roentgen rays. They concluded that an increase in mitotic activity is an effect of the irradiation on the cells and not due to changes in the irradiated medium.

The enlargement of cells and the formation of giant cells are possibly the most typical cellular reactions to irradiation that can be observed in different tissues of treated organisms.

The formation of enlarged and giant cells after roentgen irradiation was described in malignant and normal tissue of various organisms. Giant cells were described in patients irradiated for squamous cell carcinoma of the mouth and oropharynx[26] as well as in cases of carcinoma of the cervix, carcinoma of the skin, squamous cell carcinoma and epithelioma.[23] They were also noted in mice and rats following irradiation for carcinoma.[18,20,32,35]

In normal mammalian tissues, giant cells were described after irradiation in rabbits,[22,39] guinea pigs,[60] hamsters,[52] and mice.[17,40] Giant cells after irradiation were also observed in chick embryos,[55] in amphibia in tadpoles of Anura,[9,10,25] and in such Urodella as axolotl;[5,6,11,12,14,15,16] in invertebrata giant cells after irradiation were described in insects such as grasshoppers,[28,29] broconid wasp,[1] and the butterfly.[19] Giant forms after irradiation were also described in microorganisms such as protozoan Colpidium colpoda[41] and Bodo caudatus,[50] yeast cells,[3,29,61] and bacteria.[34] Giant forms were found in algae[33,44] and in Rhizopus nigricans (fungus)[37] and in the root tips of beans.[42]

Many observations of giant cell formation in tissue cultures have been made. According to Paterson[43] the enlargement of cells after irradiation was obvious by the second subcultivation of chick choroide cells and sclera cells. The cells were not all enlarged, but a varying degree of enlargement was invariably present and was seen even when the lowest doses were employed. The increased size is caused by the continued cell growth which obviously is the result of prevention of division by irradiation. Puck and Marcus[48] obtained colonial growth of mammalian cells from the single HeLa cell. After irradiation with 50 r the proportion of giant cells was 6.7 per cent; after 200 r, 23 per cent and after 600 r, 100 per cent. According to Puck and his collaborators,[49] the high metabolic activity of the giant cells was evidenced by their rapid utilization of nutrients and by their ability to synthesize protein which bounds the cells to the glass. The ability of giant cells to accept vital stains indicates the integrity of certain cellular metabolic systems. Pomerat and his co-workers[45,46] observed giant

All photomicrographs made with the same magnification (510×).

Fig. 45. Epithelium of animal 7 days after irradiation and 21 days after hatching. (E) Epithelial cells. Fig. 46. Epithelium of animal 14 days after irradiation and 28 days after hatching. (C. T.) Connective tissue cells; (E) epithelial cells. Fig. 47. Epithelium of animal 18 days after irradiation and 32 days after hatching. (C. T.) Connective tissue cells; (E) enlarged epithelial cells; (P) processes of melanophores. Fig. 48. Epithelium of animal 14 days after irradiation and 28 days after hatching. (C. T.) Connective tissue cells; (E) epithelial cells; (P) melanophores. Fig. 49–51. Epithelium of various animals 23 days after irradiation and 37 days after hatching. (E) Enlarged epithelial cells; (G) giant epithelial cells; (L. C.) Leydig's cells; (P) intraepithelial or subepithelial melanophores; (P. G.) pigment granules. Fig. 52. Epithelium of animal 28 days after irradiation and 42 days after hatching. (C. T.) Connective tissue cell; (E) epithelial cell of normal size; (G) giant epithelial cell.

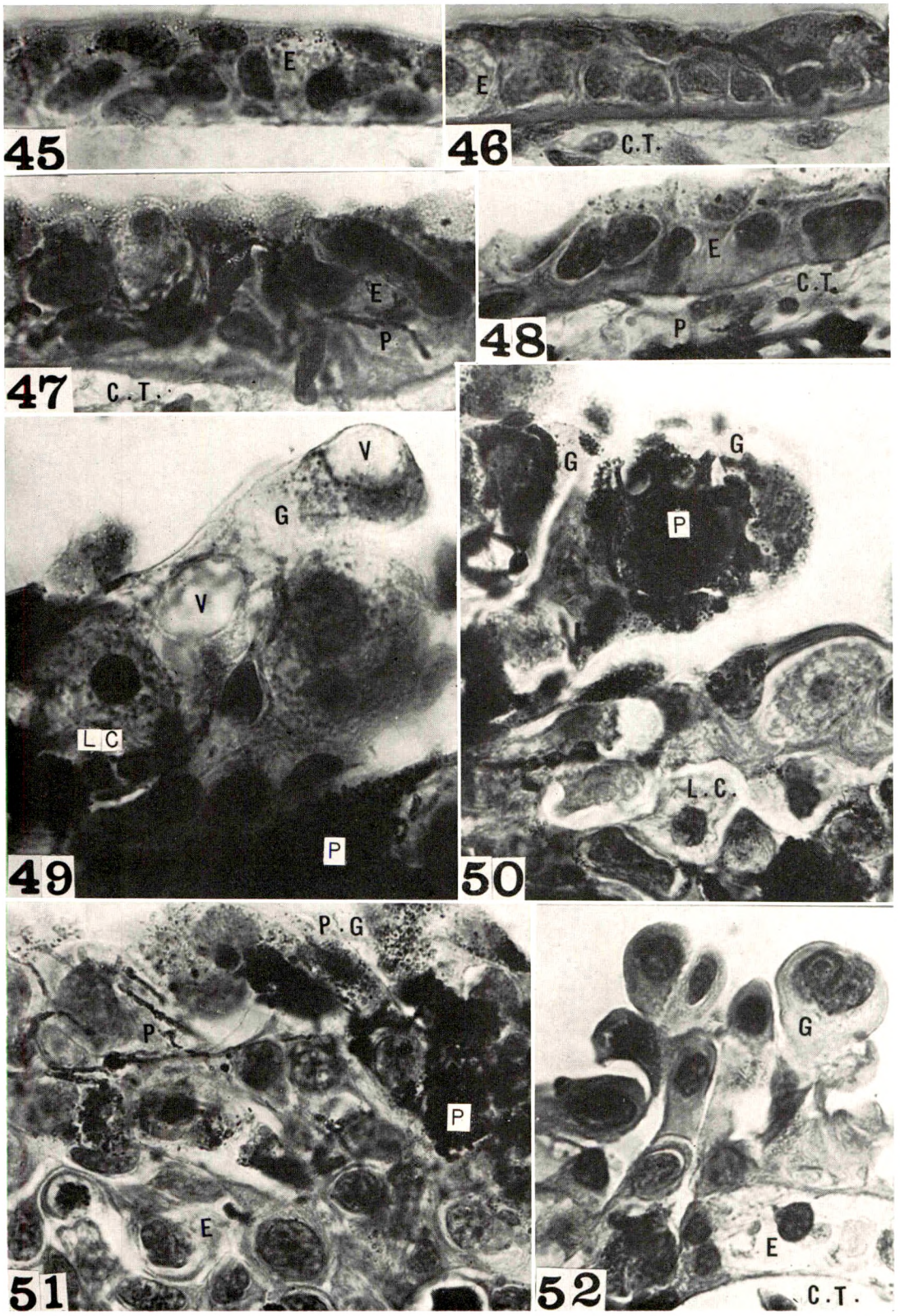


Plate viii. *Successive changes in the skin epithelium after irradiation with 6,000 r.*

cell formation in 9 species of human cell strains after exposure to 2,000 r and 4,000 r of gamma radiation from a cobalt 60 source. All the cells after irradiation were heteroploid. The observations of Pomerat and his collaborators[47] are especially important. With photomicrographs they illustrate the transformation of the same cell on the first, fifth and seventh day after irradiation. Phase contrast and time lapse cinematographic records show clearly that cell enlargement was regularly observed. Multinucleation was caused by the cells with a single nucleus, producing one or two daughter cells with numerous nuclei. Most commonly, however, gradual enlargement was observed in all the cell strains that have been studied. Such progressive increases in the mass of protoplasm are not accompanied by nuclear division. Teloreduplication, which has been defined as the simple fusion of daughter cells during or after division of cytoplasm, is relatively frequent. In some cells 6 nuclei or more were observed.[47]

Whitmore and his collaborators[62] found evidence that giant cells retained considerable metabolic function. In two strains of cells (mouse connective tissue and monkey kidney cells), it was observed that cell division was inhibited after irradiation with 5,000 r, but the majority of cells increased greatly in volume. Kohn and Fogh[31] noted in irradiated cultures cells with diameters that significantly exceeded the upper normal limit. After irradiation with 300 r about 10 per cent of the cells were larger than normal, but after irradiation with 3,000 r as many as 65 per cent were larger.

The formation and growth of giant cells in cultures of HeLa cells in response to irradiation have been determined by means of colorimetric analysis for nucleic acids and protein and by the incorporation of radioisotopes into protein deoxyribonucleic acid. The rate of incorporation of glutamic acid reached a level greater than that in control cells on a per cell basis. For a number of days, the protein synthesis extended beyond the capacity for deoxyribonucleic acid synthesis.[56] Enormous cytoplasm in the giant cells from 600 r irradiated cultures, the presence of 3 or 4 nuclei, the irregular shape of the individual nuclei with wrinkles of the nuclear membranes, and the strangely shaped nuclear masses were observed. These giant cells, although they metabolize at a rate comparable to that of an equal mass of actively dividing cells, cannot multiply.[21]

According to Schleich *et al.*[54] after irradiation multinucleated giant cells were found frequently in cultures of human tumor strains A.Fi and HeLa. Cell enlargement in cultures of HeLa cells was slightly inhibited when the dose was increased from 1,250 r to 5,000 r.[58] Individual cells with volumes over 200 times the normal have been observed in some cases.[59] The formation of giant cells was also described in Amblystoma punctatum after treatment with nitrogen mustards,[2] the effects of which are very similar to those of roentgen rays. Lea[33] stated that "If the cells are prevented from dividing but continue to grow at the normal rate, then the size of the cells will increase instead of the number."

A comparison of the giant cells of axolotl with normal cells of control animals of the same age (Fig. 3 and 19) shows that giant cells in some cases are 7 to 8 times larger than normal cells. They are 5 to 6 times

All photomicrographs made with the same magnification (510×).

Fig. 53–55. Epithelium of various animals 24 days after irradiation and 38 days after hatching. (C. T.) Connective tissue cells; (G) giant epithelial cells; (L. C.) Leydig's cell; (P) melanophores; (P. G.) pigment granules; (V) vacuoles in cytoplasm of giant cells. Fig. 56 and 57. Epithelium of various animals 28 days after irradiation and 42 days after hatching. (G) Giant epithelial cell; (P. G.) pigment granules; (V) vacuoles in cytoplasm of giant cells.

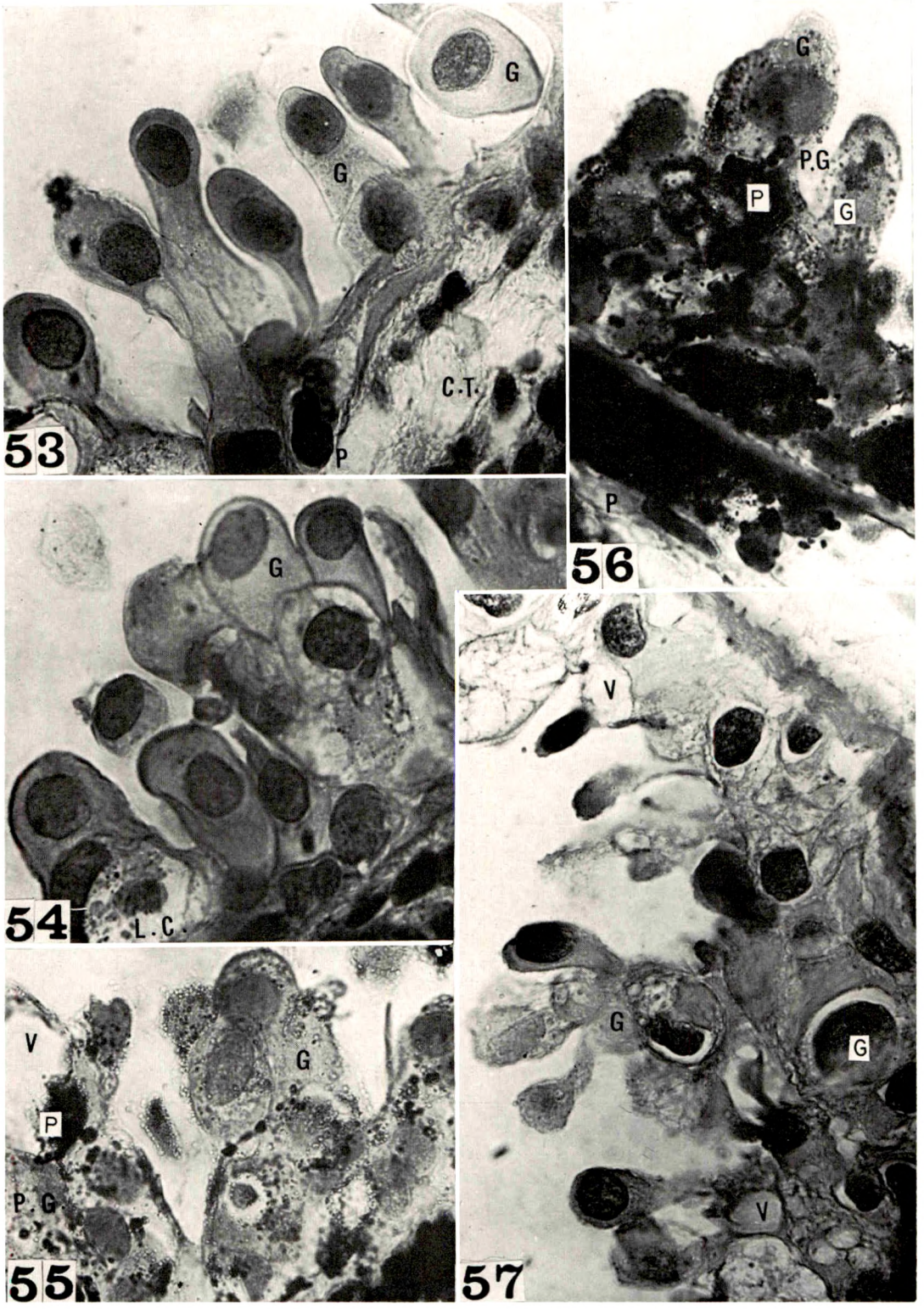


Plate ix. *Successive changes in the skin epithelium after irradiation with 6,000 r.*

larger than the other proximal epithelial cells of the same animal (Fig. 17). The nuclei of giant cells are much larger than the nuclei of normal epithelial cells. In some cases (Fig. 38) the diameter of the giant cell nucleus is 4 to 5 times larger than the diameter of normal epithelial cell nuclei of control animals of the same age. The formation of giant cells was not observed after irradiation with small doses of roentgen rays (after irradiation with 250 r), but they were observed, although not too clearly and by comparison not too enlarged, after irradiation with the largest dose (9,000 r). This was probably because the animals died too soon after local irradiation with this dose. The giant cells in corneal epithelium after irradiation never reach the size and development of those in the skin epithelium.[15] In the skin epithelium these cells are typical. The formation of vacuoles in the cytoplasm of giant cells was observed in many cases of irradiated skin epithelium (Fig. 13, 14, 38, 49, 55 and 57) but never in the epithelium of irradiated cornea. It is interesting to note that the vacuoles of the cytoplasm of giant cells after irradiation of cultures of human cells and neoplastic cells have been described by several authors.[21,24,45] Uneveness of the outer surface of irradiated epithelium was observed in both skin and corneal epithelium, but the protrusion of separate giant cells from the outer surface of the epithelium (Fig. 14, 15, 16, 17, 18, 19, 21, 29, 38, 39, 40, 41, 42, 53, 54, 55, 56, 66 and 67) which is typical for skin epithelium never reaches comparable development in the irradiated corneal epithelium. The formation of deep cracks and spaces between the epithelial cells and the complete separation of some giant cells or cell complexes have been observed in both skin and corneal epithelium.

In some instances the giant cells of skin epithelium have several nuclei (Fig. 19, 21 and 25).

SUMMARY

1. The heads of 127 animals from one spawning were irradiated 14 days after hatching with: 9,000 r, 6,000 r, 3,000 r, 1,000 r, 500 r and 250 r while 20 animals served as untreated controls.

2. No definite changes in the epithelium of the skin were observed after irradiation with 250 r.

3. Twenty-five days after irradiation with 500 r, the cells of the epithelium were slightly enlarged; 28 days after irradiation in some portion of the irradiated epithelium formation of giant cells was seen. The maximal size of the giant cells was observed 35 days after irradiation. The typical appearance of this epithelium consisted of an extremely uneven outer surface, protrusion of separate giant cells from the surface epithelium, formation of deep cracks and spaces between the cells, complete separation of some giant cells or cell complexes, and formation of vacuoles in the cytoplasm of the giant cells. Gradually, the giant cells of the degenerating epithelium were desquamated and were replaced with normal epithelium (42 and 49 days after irradiation).

4. Twenty-one days after irradiation with 1,000 r, the cells of the epithelium were definitely enlarged. Degenerating

All photomicrographs made with the same magnification (510×).

FIG. 58. Epithelium of animal 2 days after irradiation and 16 days after hatching. (C. T.) Connective tissue cells; (E) epithelial cells. FIG. 59 and 60. Epithelium of various animals 4 days after irradiation and 18 days after hatching. (C. T.) Connective tissue cells; (E) epithelial cells. FIG. 61 and 62. Epithelium of various animals 8 days after irradiation and 22 days after hatching. (C. T.) Connective tissue cells; (E) enlarged epithelial cells; (P) intraepithelial or subepithelial melanophores. FIG. 63. Epithelium of animal 9 days after irradiation and 23 days after hatching. (E) Enlarged epithelial cells; (P. G.) pigment granules. FIG. 64. Epithelium of animal 15 days after irradiation and 29 days after hatching. (G) Giant epithelial cells; (P) melanophores; (P. G.) pigment granules in cytoplasm. FIG. 65. Epithelium of animal 10 days after irradiation and 24 days after hatching. (E) Epithelial cells.

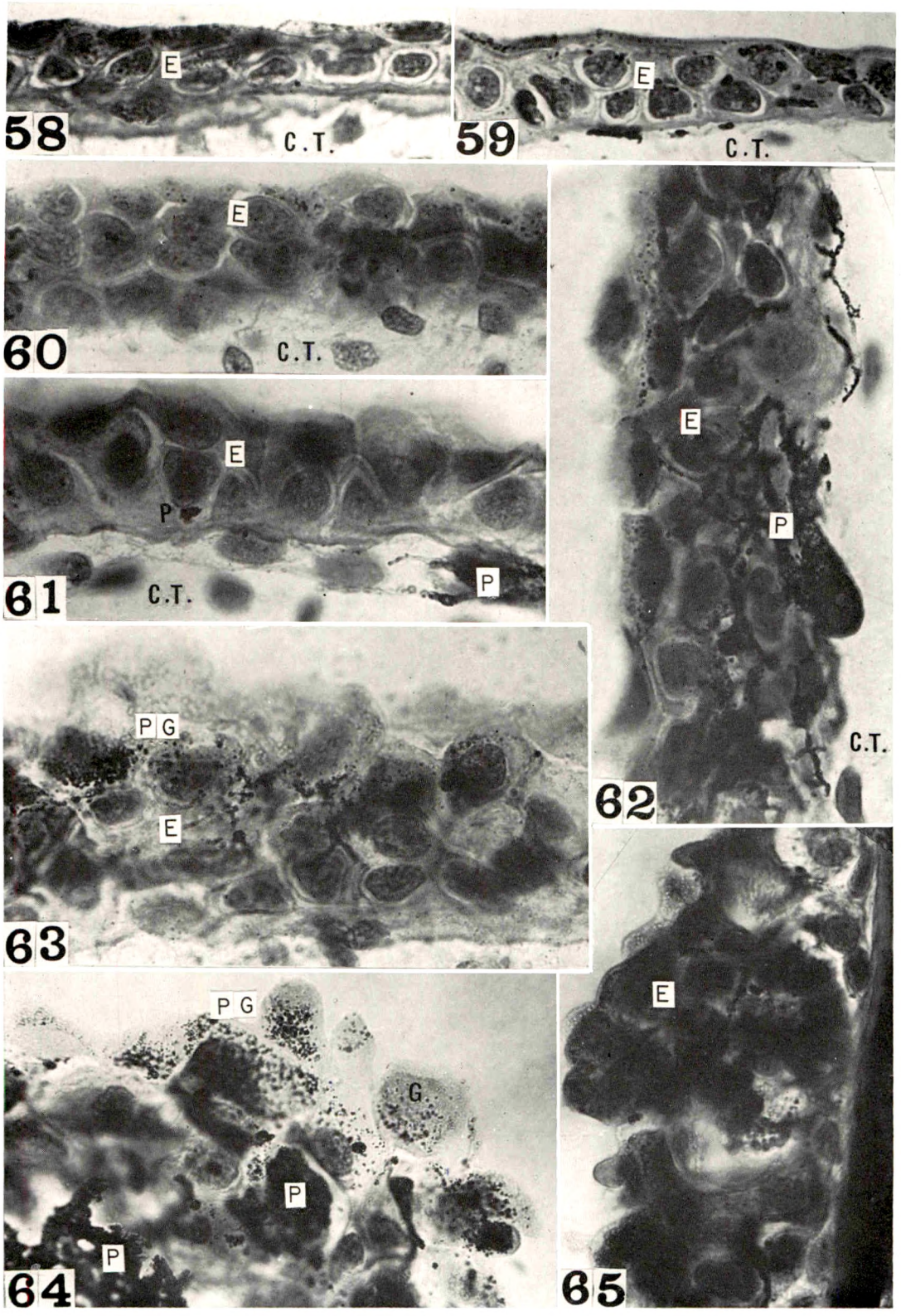


Plate x. *Successive changes in the skin epithelium after irradiation with 9,000 r.*

giant cell epithelium was observed 28 days after irradiation. This epithelium was replaced with normal epithelium 42 days after irradiation.

5. Seventeen days after irradiation with 3,000 r, the cells of the epithelium were greatly enlarged. Typical degenerating giant cell epithelium was observed 22 days after irradiation. This epithelium was replaced with normal epithelium about 42 days after irradiation.

6. Fourteen days after irradiation with 6,000 r, the cells were definitely enlarged. The formation of degenerating giant cell epithelium was observed 23 days after irradiation. The protrusion of separate giant cells was observed in especially clear form. The replacement of this epithelium with normal epithelium was not observed.

7. Eight days after irradiation with 9,000 r, the epithelial cells were definitely enlarged. In animals fixed 15 days after irradiation, the epithelium consisted only of giant cells. Only in rare cases was protrusion of separate cells from the epithelial layer observed. Vacuoles in the cytoplasm and deep cracks and spaces between the cells were observed. Replacement of such epithelium with normal epithelium was not observed.

8. Replacement of degenerate giant cell epithelium with normal epithelium occurred 40 to 50 days after irradiation with medium doses (500–3,000 r). After irradiation with larger doses, because the animals lived only 29 days (6,000 r), or even only 18 days (9,000 r), replacement of degenerate epithelium with normal epithelium did not occur.

9. The threshold of sensitivity of skin epithelium is between 250 r and 500 r.

10. Reduction of the number of pigment cells and formation of globular melanophores without processes were not observed. Subepithelial and intraepithelial melanophores were observed more often than in normal epithelium. The accumulation of pigment granules in the cytoplasm of epithelial cells was observed in many instances after irradiation with varying doses.

11. The formation of large and narrow epithelial outgrowths consisting mostly of giant cells can be considered a result of roentgen stimulation.

12. The giant epithelial cells were in some cases 7 to 8 times larger than the normal cells of control animals of the same age. They were 5 to 6 times larger than the other epithelial cells of the same animal in close proximity. The nuclei of the giant cells were much larger than the nuclei of normal epithelial cells. In some instances the diameter of the giant cell nucleus was 4 to 5 times larger than that of the nucleus of the normal epithelial cell. The maximal size and maximal development of the giant cell epithelium were observed after irradiation with medium doses.

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All photomicrographs made with the same magnification (510×).

Fig. 66 and 67. Epithelium of animal 10 days after irradiation and 24 days after hatching. (G) Giant epithelial cells; (E) enlarged epithelial cells; (L. C.) Leydig's cell; (P) intraepithelial melanophores; (P. G.) pigment granules. Fig. 68. Epithelium of animal 17 days after irradiation and 31 days after hatching. (E) Enlarged epithelial cells. Fig. 69. Epithelium of animal 18 days after irradiation and 32 days after hatching. (C. T.) Connective tissue cells; (G) giant epithelial cells; (P) melanophores. Fig. 70. Epithelium of animal 17 days after irradiation and 31 days after hatching. (C. T.) Connective tissue cells; (G) giant epithelial cell; (P) intraepithelial melanophores; (P. G.) pigment granules in cytoplasm of giant epithelial cells.

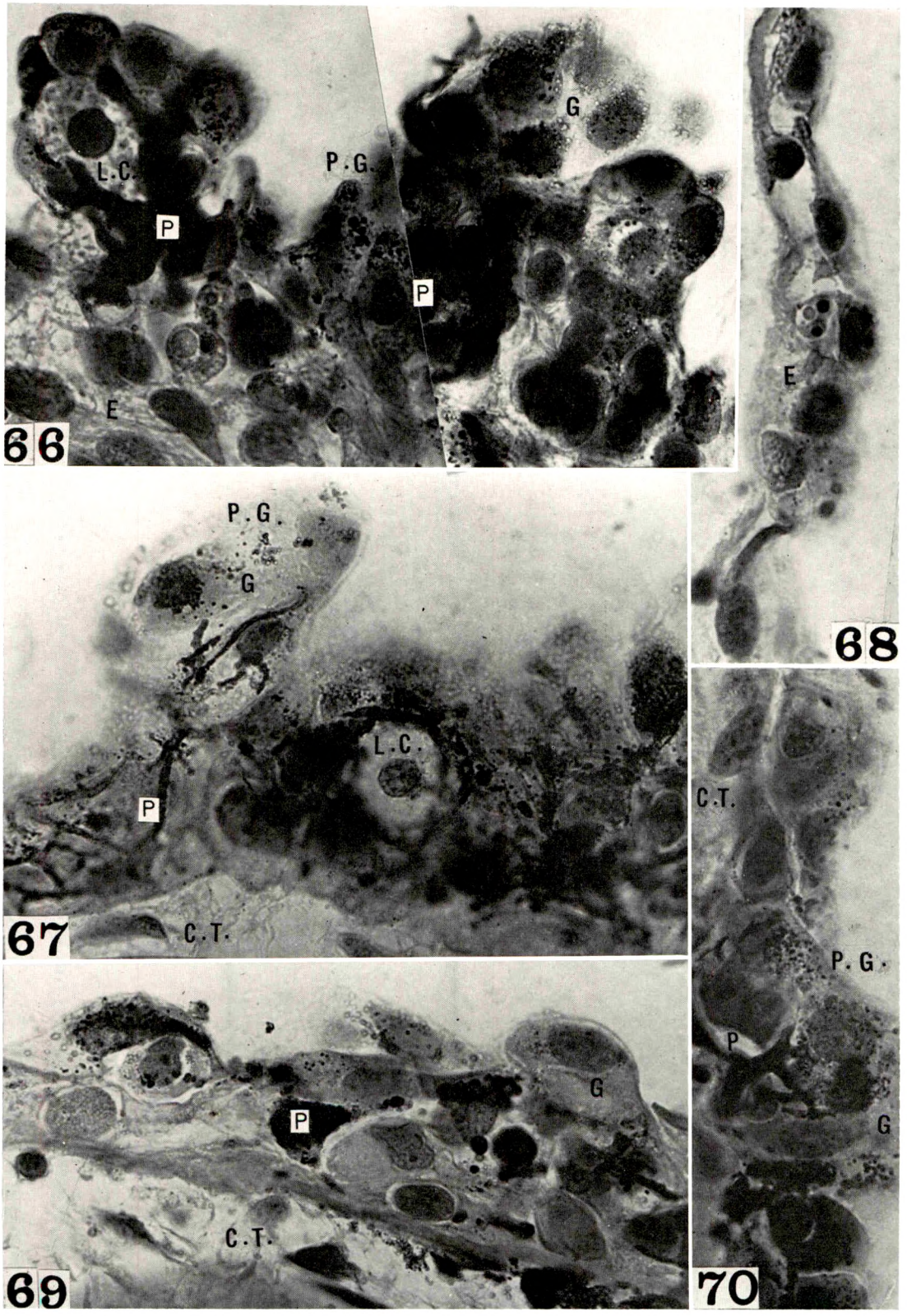


Plate xi. *Successive changes in the skin epithelium after irradiation with 9,000 r.*

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EDITORIALS

PREDETERMINATION OF AVOIDABLE OR UNAVOIDABLE RADIATION HAZARDS AND COMPLICATIONS— CALCULATED RISKS*

IF WE try to evaluate the progress of radiation therapy during the past two decades, some startling observations emerge.

First, the types of tumors for which we consider radical radiation therapy as the time-tested, consistently effective treatment of primary choice have remained essentially the same as those in which Coutard was interested. Secondly, the best statistical 5 year results in the treatment of these tumors have not changed significantly.

Excellence of treatment, therefore, is rather judged by an evaluation of the early and—more important—of the corresponding late morbidity as evidenced by the late condition of the irradiated normal tissues. Indeed, progress in radiation therapy during the last 20 years mainly consists of our greater ability to reduce tissue damage to a now negligible minimum—without compromising the effect on the tumor—through the judicious use of longer protraction and higher voltages, by our better understanding of the tolerance levels of normal structures, by greater accuracy in physical dose determination, and by better control of infection.

This advance has changed the definitions of "avoidable or unavoidable radiation hazards," but misconceptions about what is unavoidable still prevail. I shall attempt a realistic appraisal of the true magnitude of a few of the more common and frequently exaggerated risks of practical importance associated with radical radiation therapy of some of the common forms of radiocurable cancer. My conclusions are based mainly on detailed, recorded, and previously documented observations of some 3,000 patients whom I have treated and followed personally between 1939 and 1961, either alone or in close cooperation with my associates at the Swedish Hospital in Seattle and the University of California Hospitals, San Francisco, supplemented by the experiences of others whose basic treatment policy is similar to ours.

Insofar as risks depend to a considerable degree, of course, on the more or less aggressive therapeutic philosophy of the individual therapist, I shall first briefly stress some of the principles which have guided our treatment policies.

Experiences during our years of youthful enthusiasm have convinced us that an attempt to force a cancer cure by increasing the dose beyond or reducing the protraction below a "reasonable" level leads to a point of diminishing returns.

The *dose* necessary to sterilize an individual tumor and the tolerance of normal tissues in the individual patient can be appraised only by observation of response during therapy. We still believe (as we stated with Cantril and Parker[1] in 1950)

[1] BUSCHKE, F., CANTRIL, S. T., and PARKER, H. M. Supervoltage Roentgentherapy. Charles C Thomas, Publisher, Springfield, Ill., 1950.

* Presented at the Tenth International Congress of Radiology, Montreal, Canada, August 29, 1962, as part of a symposium on *Clinical Treatment Planning*.

The author wishes to express his appreciation to Dr. Robert Parker for supplying the information regarding the late follow-up observations from the Tumor Institute of the Swedish Hospital, Seattle, Washington, and to Dr. Orliss Wildermuth, Director of the Tumor Institute, for permission to use these data.

that, "A dose in the range of 5,000 to 6,000 r is sufficient to control most neoplasms which can be sterilized by ionizing radiation, and some require considerably less." Clinical and experimental evidence also indicates that the increase in dose necessary to compensate for either the lesser radiobiologic effectiveness of radiation of shorter wave lengths or for greater protraction is not so great as is still assumed by some.

In the treatment of most major radiocurable cancers, we long ago abandoned *protraction* of less than 6 weeks, and we now frequently protract treatment for 8 to 10 weeks. Therefore, I shall not discuss hazards associated with techniques using protraction of less than 5 weeks.

And, finally: The following remarks refer to experiences with supervolt techniques for external irradiation, unless specifically stated otherwise. Radical medium volt therapy for curable cancer is—with some exceptions—mainly of historic interest.

With this preamble, we recognize for the practical purpose of treatment planning two major groups of hazards, even if the pathogenetic demarcation line is not this sharp: those concerned with injury to mesenchymal tissues (vasculo-connective tissue, cartilage, bone) which, because of their distribution throughout the body must be taken into account in almost every instance of treatment planning; and those related to the radiovulnerability of specific organs.

Because of the ubiquity of the vasculo-connective tissue, its lack of reparative power, and the irreversible and often disastrous late direct and indirect effects of the more severe degrees of fibrosclerosis and vascular impairment, the radiation tolerance of the vasculo-connective tissue frequently determines the ceiling of tolerable dose. In fact, the dose of 6,000 r which somehow has come to be honored by the term, "cancerocidal," rather represents the —statistically—average limit of tolerance of the vasculo-connective tissue and, therefore, in general, the maximal safe dose. In tissues which are particularly sensitive to impairment of oxygen supply, such as the central nervous system, this average safe dose is probably lower.

In this particular phase of protection of the vasculo-connective tissue, radiation therapy has made important progress during the last two decades through the consistent use of longer protraction, supervolt therapy, and individualization by judicious exploitation of some radiobiological phenomena, to wit: the early mucosal reactions which are caused by the destruction of the surface epithelium and which occur during fractionated therapy are caused by doses that are lower than those responsible for clinically significant injury to the vasculo-connective tissue. If early mucosal reactions during and immediately following therapy are avoided or minimized, severe late vasculo-connective tissue changes usually do not occur. Our experience confirms Lederman's[2] statement that "generally the patient who does not suffer during treatment rarely encounters complications after treatment." It then follows that, wherever mucous membranes are within the irradiated volume, Nature has provided a most effective warning system: close observation for signs or symptoms of mucosal reactions during treatment and adjustment to the thereby demonstrated individual tolerance can prevent most of the significant late changes due to damage to the vasculo-connective tissues.

To substantiate these statements, I shall cite experiences in the treatment of carcinoma of the cervix, larynx, and bladder.

1. In 583 patients treated for carcinoma of the *cervix* and cervical stump at the Swedish Hospital, Seattle, between 1939 and 1956,[3] there were 7 (1.2 per cent) clinically significant instances of bowel injury —none permanently incapacitating—and

[2] LEDERMAN, M. Place de la radiothérapie dans le traitement du cancer de larynx. *Ann. radiol.*, 1961, *4*, 443–454.

[3] BUSCHKE, F. Changing place of radiation therapy in treatment of cancer. Proceedings of the Fourth National Cancer Conference. J. B. Lippincott Company, Philadelphia, 1960, pp. 183–186.

3 (0.5 per cent) late bladder ulcerations, all of which healed. There was no vesicovaginal fistula; there was one rectovaginal fistula in a carcinoma of the stump which healed after 3 years. There was no fracture of the femoral neck. The 5 year cure rate was 80 per cent in Stage I cases, 49 per cent in Stage II, and 28 per cent in Stage III. We attribute the low incidence of late complications to our deliberate attempts to avoid or minimize early mucosal reactions through greater protraction of the intracavitary radium dose (200 active hours in 2 weeks for 8,000 mg. hr. in an over-all time of 2 weeks) and through adjustment of the intracavitary and external irradiation to the individual tolerance. We do not consider a marked rectal reaction to be acceptable or unavoidable. I have not observed significant late rectal, intestinal, or bladder complications in patients who had not manifested symptoms of marked early mucosal injury.

2. Baclesse[4] has convincingly demonstrated that, using medium volt therapy, ultra-protraction markedly reduces tissue damage, yet does not compromise the sterilization of epidermoid carcinomas. In cancer of the *larynx*, his best results occurred in the group treated with a protraction of from 6 to 8 weeks. Lederman,[2] in the treatment of laryngeal carcinoma, has consistently used telecurie therapy with a *minimum* protraction of 6 weeks; he emphasizes the comfort of the patient during treatment and the rarity of late complications. "In no circumstances," Lederman states, "should a brisk or severe local reaction be callously regarded by the radiotherapist as the 'price' the patient has to pay for possible cure." In spite of this significant reduction in morbidity, he reports 5 year cure rates of 81 per cent in Stage I and 61 per cent in Stage II in 513 patients treated for Stages I and II.

In a systematic study of the treatment of carcinoma of the vocal cord which Vaeth and I[5] started early in 1958, we increased protraction by about 30 per cent without otherwise changing the 1 mev. technique: the average treatment time was extended from the previously practiced average of 40 days to 53 days for 6,000 r midline dose. The previously consistent formation of a false membrane has thus been entirely avoided, and late radiation edema has not occurred. Our collaborating otolaryngologists comment that patients "go through treatment now with amazing ease," while we formerly noted remarks in the records such as "the usual postradiation edema." As far as we can determine to date, tumor effect has not been compromised by this technique: of 21 patients treated between 1958 and 1960, 8 of 9 Stage I and 7 of 12 Stage II patients are living so far with normal larynx from $1\frac{1}{2}$ to 4 years.

3. The memory of severe fibrosis of the *bladder* during the early use of intracavitary radiation therapy still haunts the urologists. The tolerance of the bladder wall is now better understood; in particular, the investigations of Mackay[6] at the Royal Marsden Hospital, London, have again demonstrated the importance not only of total dose, but of adequate protraction.

Following the much more frequently indicated external irradiation for carcinoma of the bladder, I have not seen fibrosis with doses of 5,000 to 6,000 r delivered in 6 to 8 weeks.[1,7] None of our patients with controlled carcinoma has received higher doses than these. I have been rather impressed by the perfectly normal bladder function and capacity and by the rather minimal mucosal cystoscopic changes in patients who have lived 15 to 20 years following control of their bladder tumors. I cannot, of course, answer the question as to whether, by more aggressive external therapy, an occasional additional cure might have been

[4] Baclesse, F. Clinical experience with ultra-fractionated roentgen therapy. In: Progress in Radiation Therapy. Edited by Buschke, F. Grune & Stratton, New York, 1958.

[5] Buschke, F., and Vaeth, J. M. Radiation therapy of carcinoma of vocal cord without mucosal reaction. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1963, *89*, 29–34.

[6] Mackay, N. R. Tolerance of bladder to intracavitary irradiation. *J. Urol.*, 1956, *76*, 396–400.

[7] Buschke, F., and Cantril, S. T. Roentgentherapy of carcinoma of urinary bladder; analysis of 52 patients treated with 800 kv. roentgentherapy. *J. Urol.*, 1942, *48*, 368–383.

accomplished. From earlier experience with at times much more aggressive treatment, however, I am convinced that this would not have altered our cure rate of 16 per cent for 5 years and 13 per cent for 10 years to a statistically demonstrable degree, but that it would have increased morbidity so greatly that it might have made cystectomy preferable for these patients.

The myth still prevails—particularly in the minds of plastic surgeons—that irradiation over *cartilage and bone* is contraindicated because of the risk of necrosis. I believe, I do not have to document that healthy bone and cartilage, not compromised by tumor invasion, infection, or previous surgery, tolerate the doses necessary for the sterilization of radiocurable cancers, provided that adequate quality of radiation and sufficient protraction are used.

In 196 patients treated at the Swedish Hospital for lesions overlying the nose (recently reviewed by Parker[8]), 2 instances of cartilaginous necrosis were observed, both with uncontrolled disease (1 per cent). Following the treatment of 39 carcinomas of the skin of the auricle, reported by Parker and Wildermuth,[9] there were 3 instances of cartilaginous necrosis, all associated with tumor invasion of cartilage or with uncontrolled disease.

Our more recent experiences with radical preoperative irradiation for oral lesions, followed by radical surgery,[10] have shown that the mandible, resected up to 6 months after doses as high as 8,000 r, was not grossly distinguishable from nonirradiated bone, and free bleeding was encountered even when the transection passed through the treatment field. Also there were 2 instances in which laryngofissure and cordectomy following radiation therapy were done without cartilaginous slough or other complications.

That apparently we have been plagued by fewer complications due to injuries of mesenchymal tissues than might have been our expected share resulted perhaps from the fortuitous circumstance that, beginning in the early 1940's (heeding some bitter earlier experiences) we tended more and more towards greater protraction of treatment time. This may also be one reason why we have been less impressed by the importance of *radiation myelitis* than other therapists seem to be. We have perhaps rather unintentionally avoided this complication.

Among 125 patients treated at the Swedish Hospital for cancer of the nasopharynx, tonsil, and base of tongue between 1944 and 1956, 6 developed neurologic symptoms and signs which were interpreted as due to cervical radiation myelitis.[8,11] From retrospective analysis of the records, I would estimate that the dose delivered to the spinal cord in these instances was in the average range of 7,000 to 8,000 rads in approximately 50 days. Three of these 6 patients recovered without residual symptoms, 2 remained stationary but not incapacitated until death, 5 and 8 years later, and in 1 symptoms have persisted for 13 years.

The radiation tolerance of the *central nervous system* is still not well established. From a practical viewpoint, it would seem reasonable today to assume that a dose to the spinal cord in the range of 5,000 r represents about the limit of safety.[12] On the other hand, we have seen patients who have obviously tolerated higher doses. We have also encountered some who had significant neurologic symptoms after considerably lower cord doses. These patients exhibited also a lesser than average tolerance of the mucous membranes. Subclinical asymptomatic neurologic deficits would probably be found more frequently through systematic neurologic examination.

[8] Parker, R. G. Personal communication—June 26, 1962.

[9] Parker, R. G., and Wildermuth, O. Radiation therapy of lesions overlying cartilage. I. Carcinoma of pinna. *Cancer*, 1962, *15*, 57–65.

[10] Buschke, F., and Galante, M. Radical preoperative roentgen therapy in primarily inoperable advanced cancers of head and neck. *Radiology*, 1959, *73*, 845–848.

[11] Cantril, S. T. Personal communication—September 26, 1957.

[12] Lampe, I. Radiation tolerance of central nervous system. In: Progress in Radiation Therapy. Edited by Buschke, F. Grune & Stratton, New York, 1958.

In contrast to the "avoidable" hazards discussed so far, there is a group of unavoidable radiation injuries which must be considered as an acceptable price—comparable, for instance, to the loss of anal function in the surgical treatment of rectal carcinoma. I mention only one example: injuries to the *eye*.

I am carrying coals to Newcastle by stating here that complete protection of all ocular structures by insertion of appropriate shields beneath the lids is a simple routine in situations where the orbit is not involved (for instance, in treatment of carcinoma of the eyelids). If, however, a neoplasm encroaches on the orbital walls or involves the orbit (for instance, in the treatment of some tumors of the paranasal sinus), complete protection of the eye is not possible without the risk of protecting tumor. Injury to the lens is not considered in these circumstances since the delivery of cataractogenic doses is unavoidable and cataract is a small price to pay. We are rather concerned in these situations with radiation injury to the cornea. Concluding from our observations of 23 patients who received direct irradiation to the eye[8,13] (ranging from 1,650 rads in 11 days to 6,000 rads in 29 days), it appears that direct corneal exposure to radiation of supervolt quality as high as 2,000 to 2,500 r has been tolerated. With 3,000 r, we have seen transient keratitis. In 3 patients who received corneal doses of 6,000 r, we observed permanent corneal opacity with ground glass appearance, ocular phthisis, enophthalmos, and, in 1 instance, perforation. The severe pain associated with these changes necessitates enucleation, and we have become doubtful as to whether our previous policy of preliminary enucleation even of a good eye is not preferable when high corneal doses seem unavoidable for adequate treatment. Sometimes, however, such severe injury can be avoided by the insertion of a small lead shield in the beam, which casts a shadow on the cornea only.

In conclusion, it is suggested that, in general, morbidity and functional impairment associated with properly indicated and competently executed radiation therapy are far less serious than those accepted as a matter of course in the surgical treatment of many forms of cancer. Many misconceptions regarding the hazards associated with radiation therapy result from insufficient differentiation between the 3 types of tissue injury caused by ionizing irradiation: (1) Injuries under experimental conditions which are not comparable to any clinically used techniques. These are, of course, interesting only from the standpoint of radiation pathology and biology; (2) injuries following clinical therapy with techniques now considered inappropriate; and (3) injuries associated with legitimately indicated and technically competent therapy, as judged by present standards.

To consider injuries which we all still remember from the days of radiation therapy's infancy and puberty in the indications for radiation therapy of today is tantamount to basing present surgical indications on the morbidity and mortality of the pre-Listerian era. The greatest single hazard remains the poorly trained radiation therapist.

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[13] Cantril, S. T. Personal communication—September 11, 1957.

POLAROID LAND PHOTOGRAPHY IN A RADIATION THERAPY DEPARTMENT

POLAROID Land photography in a radiation therapy department, where many patients are examined and treated daily and return for subsequent follow-up observations, has many applications which have proved of extreme value. It is our practice to have each new patient photographed by a resident physician or by a nurse. This quickly obtained and inexpensive photograph is stapled to the inside cover of the patient's record for ready reference. No patient has objected to this procedure. If used only as an aid in associating the patient with the disease, the purchase of the camera is justified.

In most radiation therapy departments, a diagram of the body area to be treated is sketched or stamped in the record. Over this sketch are outlined the location, size, and position of the treatment field. The inherent inaccuracies of such a system are particularly obvious when tumor recurs near or within suspected margins of previously treated fields.

In the era of medium volt roentgen therapy, skin pigmentation, atrophy, telangiectasis, and epilation were clues to previously treated areas. When these showed correlation with the diagram of the field, they assumed even greater importance. With properly administered supervolt therapy, however, the tissues are spared and skin changes seldom occur. Since the skin has lost its once useful function of identifying treatment fields when a patient is treated with supervolt equipment, the actual treatment fields outlined by the light-localizing device on the therapy machine, or the skin markings, are photographed for documentation. The photograph of the fields is obtained with the patient in correct position for treatment. Complicated treatment positions are also photographed so that the technician and resident may place the patient in the original treatment position each day. These photographs, likewise, are incorporated into the patient's permanent medical record.

Visible lesions, as for example, lip and skin carcinomas, are photographed before, during, and after treatment. Since location, regression, or progression of large lymphadenopathies under treatment is often misjudged, photographs for correlation with written data serve as useful supplements. Patients whose lesions require more detailed color photography are sent to a professional photographer.

Roentgenograms, particularly those used for teaching, occasionally become misplaced or lost. Roentgenograms may be easily photographed with a Polaroid Land camera, directly from a viewbox without special duplicating cameras or apparatus. These duplicates are of excellent and permanent quality and of great value in the patient's record. Roentgenograms of lesions of the chest, bone, gastrointestinal tract, and of other regions, before, during, and after treatment lend themselves to effortless duplication without professional processing. We have frequently photographed an extremity in which a neoplasm was present and then correlated these photographs with Polaroid reproductions of the patient's roentgenograms. A copy in the record also expedites the return of the original roentgenogram to the referring physician. Electrocardiograms and visual field charts for inclusion in the treatment record are copied satisfactorily from hospital records by Polaroid photography. Gross specimens, both surgical and postmortem, can also be photographed quickly and thus be included in the patient's record. Such photographs further add to the completeness of the medical record, increasing its value for subsequent review of the disease entity.

With Polaroid Land projection film, type 46.L, the same camera produces excellent transparencies of visible lesions, equip

ment, roentgenograms, and printed pages from publications which are used for projection slides in lectures. These transparencies are fitted into plastic covers which are lightweight, unbreakable, and reusable—advantages appreciated particularly by the lecturer who travels by airplane.

With the use of the Polaroid Land camera, elaborate lighting devices occupying valuable space are not necessary. The rapid development of photographs, without requiring dark room facilities, is yet another advantage of this type of photography.

In summary, Polaroid Land photography can be adopted for routine use in a department of radiation therapy for multiple purposes. These are: patient identification; documentation of treatment set-up and field positioning; illustration of lesions before, during, and after treatment; reproduction of roentgenograms and hospital chart data; photography of pathologic specimens; and preparation of projection slides.

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ARTHUR W. FUCHS
1895-1962

ARTHUR W. FUCHS, honorary member of the American Roentgen Ray Society, internationally known authority on X-ray procedures, and a member of the X-ray Sales Division of the Eastman Kodak Company for 33 years, died in Rochester, New York, October 7, 1962, after a short illness.

Mr. Fuchs was born in Chicago, Illinois. He was the son of Wolfram C. Fuchs, one of the leading early American radiographers. He matriculated at the University

of Chicago, but his education was twice interrupted; once for military service on the Mexican border, and again for duty in the United States Army during World War I. His initial training in radiography was received in 1918 at the Military School of Roentgenology, Cornell Medical School, New York, New York.

His career had many facets. He joined Kodak in 1927 as an x-ray technical representative. In 1930, he was appointed correspondent with the added duties of supervising the testing of x-ray film carried on by the X-ray Sales Division, the editing of the company's periodical publication *Radiography and Clinical Photography* (now, *Medical Radiography and Photography*) and the editing of its two radiographic manuals *X-rays in Medicine* (now, *The Fundamentals of Radiography*) and *X-rays in Dentistry*. A major contribution was the series of 26 articles he published between 1930 and 1941 on radiography of the skull and vertebral column. In 1934 he made the first radiograph of a living person on one sheet of 32 by 72-inch x-ray film, using compensating filters and a single exposure. Several technics he devised are now ascribed to him in radiographic reference works. He also did practical research on many other aspects of medical radiography including x-ray exposure factors and the processing of x-ray film.

Because of his reputation as an authority on radiography, Mr. Fuchs was requested by the U. S. Army to participate in its program for training x-ray technicians during World War II. Granted a leave of absence by Kodak in March, 1941, he was commissioned a Major in the Sanitary Corps and appointed Chief of the X-ray School at the Army Medical Center in Washington. He established an accelerated training program for about 700 x-ray technicians. For that program, he devised the "optimum kilovoltage technic," which was subsequently standardized for use with the U. S. Army x-ray field apparatus. He also perfected the standardized exposure procedure used by the Army for photoradiography.

Upon his return to the company in 1945, Mr. Fuchs was appointed supervisor of Kodak's Medical Technical Services and assumed the duties of correspondent, lecturer, and technical advisor. He was in great demand as a lecturer before local, state, and national x-ray societies; for several years he presented a series of refresher courses at annual meetings of the American Society of X-ray Technicians and the Canadian Society of Radiological Technicians.

Mr. Fuchs was the author of 75 articles and 3 books on radiographic principles, technics, and other subjects, including the history of x-ray film, a subject that captivated his interest during much of his career. His book *Principles of Radiographic Exposure and Processing*, printed in 1958, has become a standard reference.

Mr. Fuchs was an honorary member of the American Society of X-ray Technicians and a recipient of its Jerman Memorial Medal. He was also a Fellow of the Biological Photographic Association, an honorary life member of the Canadian Society of Radiological Technicians, and a member of the Photographic Association of America, the Society of Photographic Scientists and Engineers, the Association of Military Surgeons, the Reserve Officers Association, the Retired Officers Association, and the American Legion. He received his honorary membership in the American Roentgen Ray Society in 1961.

Following his retirement from the Eastman Kodak Company in January, 1961, Mr. Fuchs was appointed to the Advisory Committee of the George Eastman House of Photography, Rochester.

Mr. Fuchs is survived by his widow, daughter, son, and nine grandchildren.

W. S. Cornwell

BOOK REVIEW

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Surgery of the Esophagus. By Raymond W. Postlethwait, M.D., Professor of Surgery, Duke University Medical Center, Chief of Surgery, Veterans Administration Hospital, Durham, North Carolina; and Will Camp Sealy, M.D., Professor of Thoracic Surgery, Chief, Division of Thoracic Surgery, Department of Surgery, Duke University Medical Center, Durham, North Carolina. Cloth. Price, $30.00. Pp. 482, with 201 illustrations. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1961.

As the authors state in the preface, surgery of the esophagus has undergone less dramatic change than that of the rest of the thoracic field. Principally devoted to surgical consideration of esophageal diseases, this book goes much further, presenting pathologic and anatomic descriptions. It is enriched with hundreds of good references, chronologically arranged in every segment of each chapter, and listed alphabetically at the end of each chapter. The extensive research by the authors of the American and foreign literature is indicated by some 684 quoted references on the subject of squamous cell carcinoma of the esophagus.

Essentially, this book is intended for the thoracic surgeon; a general practitioner, however, would find it helpful for reference and internists would be interested in the collagen and rheumatic diseases. Esophagitis and hiatus hernia are other conditions in which responsibility is shared by the surgeon and internist. The organization of each chapter is excellent, beginning with historical high points, etiology, pathology, subjective and objective clinical findings, radiologic study, and ending with the therapy of each disease.

The radiologist will find a special section in each chapter, illustrated by superb roentgenographic reproductions. Radiation therapy of esophageal carcinoma is also discussed.

The surgical technique is well detailed. Up to date information, such as new views on the etiology of achalasia or new concepts on esophageal replacement, is presented. The authors give the reader their opinions on each disease, especially regarding therapy, documenting them with a fairly large series of cases seen at the Duke Medical Center in the last thirty years. Other concepts, not necessarily shared by the authors, are also mentioned.

Esophageal varices are discussed less extensively but in a very competent manner and there is a section on splenoportography with the technique well outlined.

The book ends with a review of the anatomy and physiology of the esophagus, the latter being the latest knowledge on the subject.

Domenico Scarano, M.D.

BOOKS RECEIVED

Principles of Chest X-Ray Diagnosis. Second edition. By George Simon, M.D., F.F.R., Assistant Director, X-Ray Department, Brompton Hospital, London; Radiologist, St. Bartholomew's Hospital, London; Demonstrator, Radiological Anatomy, St. Bartholomew's Hospital, London; and Curator of the Radiological Museum and Teacher of Radiology, The Institute of Diseases of the Chest, University of London, London, England. Cloth. Price, $8.75. Pp. 207, with 200 illustrations. Butterworth, Inc., 7235 Wisconsin Avenue, Washington 14, D. C., 1962.

Synopsis of Roentgen Signs. By Isadore Meschan, M.A., M.D., Professor and Director of the Department of Radiology at the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina; Formerly Professor and Head of the Department of Radiology at The University of Arkansas School of Medicine, Little Rock, Arkansas; with the assistance of R. M. F. Farrer-Meschan, M.B., B.S., M.D., Melbourne, Australia. Cloth. Price, $11.00. Pp. 436, with 465 illustrations. W. B. Saunders Company, West Washington Square, Philadelphia 5, Pa., 1962.

Proving Ground; An Account of the Radiobiological Studies in the Pacific, 1946–1961. By Neal O. Hines. Cloth. Price, $6.75. Pp. 366. University of Washington Press, Seattle 5, Washington, 1962.

Actions of Radiations on Living Cells. Second edition. By the late D. E. Lea. Paper. Price, $2.95. Pp. 416, with figures and charts. Cambridge University Press, American Branch, 32 East 57th Street, New York 22, N. Y., 1962.

Darmchirurgie; Klinik, Indikation, Technik,

Prognose. By Professor Dr. med. M. Reifferscheid, Oberarzt der Chirurgischen Universitätsklinik, Bonn, Germany. Cloth. Pp. 372, with 410 illustrations. Georg Thieme Verlag, Stuttgart, Germany. In the U.S.A. and Canada: Intercontinental Medical Book Corporation, New York 16, N. Y., 1962.

Isodose Charts and Depth Dose Tables for Medium Energy X Rays. Prepared by K. C. Tsien and M. Cohen, Ph.D., in collaboration with the Radiotherapy Department of Temple University Medical Center, Philadelphia, Pa., and the Scientific Sub-Committee of the Hospital Physicists' Association, United Kingdom. Paper. Price, $29.50. International Atomic Energy Agency, Vienna, Austria, 1962.

Proceedings of the Third International Conference on Medical Electronics, London, 1960. Cloth. Price, $34.50. Pp. 535, with many illustrations. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Illinois, 1962.

Modern Radiology in Historical Perspective. By Stephen B. Dewing, M.D., Director of Radiology, Hunterdon Medical Center, Flemington, New Jersey; Associate Clinical Professor of Radiology, New York University Post Graduate Medical School, New York, New York. Cloth. Pp. 189. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1962.

Technological Needs for Reduction of Patient Dosage from Diagnostic Radiology. A symposium held under the auspices of the Division of Radiological Health, United States Public Health Service, Washington, D. C., March 5–6, 1962. Edited by Murray L. Janower, Department of Radiology, Massachusetts General Hospital, Boston, Mass. Cloth. Price, $6.75. Pp. 337 with many illustrations. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1962.

Malpractice Law Dissected for Quick Grasping. By Charles L. Cusumano, Member of New York Bar. Cloth. Pp. 132. Medicine-Law Press, Inc., 42 Broadway, New York 4, N. Y., 1962.

Bone Marrow Therapy and Protection in Irradiated Primates. Proceedings of a symposium, August 15–18, 1962. Paper. Price, $4.00. Pp. 458, with numerous illustrations. Radiobiological Institute of the Organization for Health Research T. N. O., 151 Lange Kleiweg, Rijswijk (Z. H.), The Netherlands, 1962.

Die Röntgendiagnostik der Lunge. By Dr. L. Babaiantz,✤ ehemaliger Professor, Medizinische Fakultät der Universität Lausanne, Switzerland; and Dr. F. Cardis, Lehrbeauftragter, Medizinische Fakultät der Universität Lausanne, Switzerland. Paper. Pp. 90, with 48 illustrations. Georg Thieme Verlag, Herdweg 63, Stuttgart, Germany. In the U.S.A. and Canada: Intercontinental Medical Book Corporation, New York 16, N. Y., 1962.

Rendiconto dell'Attività; Nel Quinquennio Accademico 1955–1960. By Prof. Enrico Benassi, Istituto di Radiologia dell'Università di Torino, Italy. Paper. Pp. 126. Tipografia Odello, 1962.

L'Angiographie de L'Artère Carotide Interne; Chez le Sujet Normal. By D. Dilenge. Paper. Pp. 230, with 156 illustrations. Masson et Cie, Éditeurs, Paris, France, 1962.

The Scandinavian Journal of Clinical & Laboratory Investigation. Vol. 14—Suppl. 63. Effect of Acute Hypoxia on Renal Haemodynamics and Water Diuresis in Man. By Per-Ola Granberg. Paper. Pp. 62. Department of Clinical Physiology, Surgery and Urology, Karolinska Institutet, Medical School, Karolinska Sjukhuset, Stockholm, Sweden, 1962.

The Scandinavian Journal of Clinical & Laboratory Investigation. Vol. 14—Suppl. 64. Special Issue for Bertil Josephson on the Occasion of His Sixtieth Birthday. Paper. Pp. 113. Oslo, 1962.

The Scandinavian Journal of Clinical & Laboratory Investigation. Vol. 14—Suppl. 65. Quantitative Analysis of Enzymes in Normal and Diseased Kidney Tissue. Å. Holmgård, M.L., Central Laboratory, St. Erik's Hospital, Stockholm, Sweden. Oslo, 1962.

Acta Orthopaedica Scandinavica. Suppl. 55. Contrast Examination of Lumbar Interspinous Ligaments. By Rolf Köhler. Paper. Pp. 64. Ejnar Munksgaard, Copenhagen, Denmark, 1962.

Acta Orthopaedica Scandinavica. Suppl. 57. Surgery of Acute Arterial Injuries in Connection with Fractures and Dislocations. By Erkki V. S. Koskinen. Paper. Pp. 43. Ejnar Munksgaard, Copenhagen, Denmark, 1962.

Acta Orthopaedica Scandinavica. Suppl. 58. Role of Surgical Interventions of the Hip Joint in the Aetiology of Aseptic Necrosis of the Femoral Head; Experimental Study. By Pentti Rokkanen. Paper. Pp. 107. Ejnar Munksgaard, Copenhagen, Denmark, 1962.

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ROENTGEN DIAGNOSIS

HEAD

GALLIGIONI, F., and RUFFATO, C. Il pneumoencefalo da osteoma fronto-etmoidale. (Pneumoencephalus secondary to a fronto-ethmoidal osteoma.) *Radiol. med.*, May, 1962, *48*, 447–460. (Address: Dott. Ferdinando Galligioni, Via Scardeone, 26, Padova, Italy.)

A rare case of intracerebral pneumatocele secondary to an osteoma of the fronto-ethmoidal structures is presented. Twenty-five similar cases have been reported in the literature.

The formation of the aerocele is determined by pressure necrosis of the walls of the paranasal sinuses and profound alteration of the mucosa produced by the slow growing osteoma. This process eventually may provoke discontinuity of the dura mater. The air penetrating into the cerebral cavity may give rise to intracerebral or extracerebral collections, *i.e.*, extradural, subdural, subarachnoid, intracerebral and intraventricular. Multiple localizations of the air may occur.

The authors demonstrated roentgenographically the intracranial pneumatoceles in the frontal region and in the lateral ventricle.—*Anthony A. Blasi, M.D.*

KLAUS, E. Spasmus facialis mit Hochstand der Felsenbeinpyramide im Rahmen basilärer Impressionen. (Facial spasm with high position of petrous pyramid associated with basilar impressions.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, July, 1962, *97*, 23–32. (Address: Pavlovstrasse 13, Olomouc, Czechoslovakia.)

Findings of basilar impression only have been of academic interest in the past. In recent years, however, decompression operations have succeeded in relieving many associated signs and symptoms. Basilar impression can be asymptomatic, but it may also simulate multiple sclerosis, amyotrophic lateral sclerosis, bulbar paralysis, cerebellar lesions and other conditions.

The osseous dysplasia is also encountered in association with maldevelopment of nerve structures. Occasionally it is observed together with true unilateral facial spasm which represents a rare facial nerve irritation. The author has observed 9 such cases. In 3 of these, the petrous pyramid on the affected side was higher than on the contralateral side. The roentgen findings of the skull and cervical spine are discussed in detail.

Unilateral elevation of the petrous pyramid is insignificant in the majority of instances, especially when asymptomatic. When, however, it is seen together with a basilar impression it may contribute to the development of ipsilateral facial spasm and is not merely coincidental. It has also been observed together with trigeminal neuralgia.—*Ernest Kraft, M.D.*

LUESSENHOP, ALFRED J., GIBBS, MARTIN, and VELASQUEZ, ALFREDO C. Cerebrovascular response to emboli; observations in patients with arteriovenous malformations. *A.M.A. Arch. Neurol.*, Oct., 1962, *7*, 264–274. (Address: Dr. A. J. Luessenhop, Georgetown University Hospitals, 3800 Reservoir Road, Washington, D. C.)

Small plastic emboli, introduced into the cervical carotid or vertebral arteries, have been employed in the treatment of large cerebral arteriovenous malformations. The increased caliber and flow of the primary feeding arteries provide a favorable hemodynamic situation which directs the free passage from cervical arteries to the enlarged, abnormal vessel provided the emboli are too large for acceptance by the smaller branches to the surrounding normal brain.

The passage of 471 plastic emboli in 11 patients was studied and roentgenographic observations regarding the immediate and delayed response of the larger leptomeningeal arteries were made. Seriographic angiograms of both carotid and vertebral arteries provided information concerning the primary feeding arteries, active and potential collaterals, the angle of branching and sites of narrowing due to plaques. Arterial diameters were determined to 0.1 mm. and corrected for image magnification. These considerations determined the appropriate size for the plastic spheres which were designed to lodge at the arterial origin of the malformation. Serial angiograms and plain roentgenograms were used throughout the procedure to check the position of the opaque emboli and the effects on the vessels. A film which could be processed rapidly was found helpful.

The response to an embolus depends upon the nature of the particle and the anatomic and hemodynamic characteristics of the vascular channels. Individual variation in the structure of collaterals and functional changes in arterial diameter made embolization a dynamic process. The course of the embolus is, to a large extent, influenced by its tendency to remain in the major conduits provided by the internal carotid and its anatomic continuation, the middle cerebral trunk. Many angiograms showed direct passage of the particle to the desired site at the malformation where it was passively accepted without spasm. Dilatation of the major feeding artery proximal to the point of occlusion was noted on occasion. Transient arrest of the particle at arterial branchings proximal to the malformation may occur in the presence of atheromatous narrowing or marked tortuosity and may last for minutes or

days. Brief arrest was not clinically perceptible but long interruption of the flow to normal brain produced neurologic deficit which was reversible. Angiography allowed correlation between these clinical events and the location of the embolus.

The observations suggest that a leptomeningeal artery accepts a bland embolus passively. Transient arrest occurs at bifurcations and, after a brief period, there is dilatation of the artery both proximal and distal to the point of impaction which may permit further progress. With the eventual, permanent lodgement of the particle, dilatation proximal to the point of occlusion occurs and may persist for many days.—*Jack Reynolds, M.D.*

Allcock, J. M. Vertebral angiography: its accuracy in the diagnosis of intra-cranial space-occupying lesions. *J. Canad. A. Radiologists*, June, 1962, *13*, 65–69. (From: Victoria Hospital, London, Ontario, Canada.)

The findings in 106 patients on whom vertebral angiography has been performed during the last 6 years are discussed. In most of these, direct arterial puncture was employed as it was felt that opacification with subclavian punctures or retrograde aortic catheterization produced roentgenorgams of relatively poor quality. Of the entire series, 10 examinations were technical failures, 10 were visualized in only one plane, and 86 were good quality biplane examinations.

The angiographic findings in the 96 cases were as follows: definite mass, 32; probable mass, 7; vascular anomaly, 17; and negative, 40. Angiographic accuracy tables show that of the 32 cases diagnosed as definite mass, 28 were proved cases. Of the 7 diagnosed as probable mass, 3 were proved, 2 were not proved, and 2 were incorrect. Of the 31 proved cases correct localization was provided in 29.

The pathologic findings of the 31 cases were: glioma, 8; aneurysm with hematoma, 6; acoustic neuroma, 4; intracerebral hemorrhage, 3; angioma with hematoma, 3; hemangio-endothelioma, 2; metastasis, 2; ependymoma, 2; and meningioma, 1.

The many difficulties associated with vertebral angiography in mass localization are discussed, but the well documented figures indicate that this approach can be very helpful if its limitations are clearly understood.—*Joseph H. Allen, M.D.*

Bell, Robert L., and Hertsch, George J. The determination of cerebral circulation time. *J. Nuclear Med.*, Sept., 1962, *3*, 399–406. (From: The Section of Neurological Surgery, US Consolidated Center Hospital, Wadsworth Division, Wadsworth, Kan.)

The authors have devised a system for measuring cerebral circulation time in which one counter with a small collimated detection crystal is placed over the internal carotid artery and a second over the confluence of the venous sinuses of the brain. Their studies have been made in conjunction with, but following, internal carotid arteriography performed in the usual manner. In a small experience there has been good correlation between circulation time measured by the radioisotope method and that which can be deduced from the roentgenograms. Tracer doses of 100 μc of I^{131} HSA or of Hg^{203} neohydrin have been employed and afford adequate counting rates.

An interesting aspect of the instrument system is the use of a two-channel magnetic tape recorder for data storage, a technique becoming increasingly popular in the field of nuclear medicine.—*Frederick J. Bonte, M.D.*

Oldendorf, W. H. Measurement of the mean transit time of cerebral circulation by external detection of an intravenously injected radioisotope. *J. Nuclear Med.*, Sept., 1962, *3*, 382–398. (From: The Neurology Section, Wadsworth General Hospital, Los Angeles Veterans Administration Center and the Division of Neurology, University of California, Los Angeles, Calif.)

Mean circulation time, measured with a radioisotope tracer, is used as an index of the blood supply of each hemisphere of the brain. The author seeks to avoid physiologic complications which might result from carotid artery puncture and intra-arterial injection, and administers the tracer (400 μc of I^{131} hippuran) into an antecubital vein. With a blood pressure cuff, he attempts to produce a compact bolus of tracer by obstructing the vein proximal to the injection site. After the injection is completed the still-inflated cuff is suddenly removed. It is interesting to note that studies of the shape of the bolus in the arterial circulation of the neck, done by a contrast medium method, indicate that the bolus has streamed considerably by the time it has reached the internal carotid artery.

Passage of the tracer through the cerebral circulation is measured by two pairs of scintillation detectors applied in the frontal and occipital regions, respectively. There is lateral shielding about both counters, and there is midline shielding between the two members of the pair. The preamplifier outputs from the right front and back photomultiplier tubes are mixed and fed to one discriminator-rate meter system, and the outputs of the two left detectors are similarly connected. Two pairs of dual channel recorders are employed. The first pair records the output of the rate meters, while the second pair plots the first derivative by means of a capacitor. The author feels that the first derivative information is the more useful. With this system he has studied 15 normal men, and has found circulation times of 6.5 to 10 seconds. These findings are in agreement

with the observations of other authors.—*Frederick J. Bonte, M.D.*

Neck and Chest

Brown, E. L. (St. Thomas, Ontario, Canada.) Histoplasmosis in Southern Ontario: a further report. *Canad. M. A. J.*, Sept. 8, 1962, *87*, 545–551.

Histoplasmosis is common in Southern Ontario. In St. Thomas, Ontario, 79 per cent of a random group of 400 long time residents had a positive reaction to histoplasmin skin testing. A combined histoplasmin skin testing, tuberculin testing and roentgenographic examination program was carried out in Elgin County, Ontario, and it was found that the percentage of positive histoplasmin reactors in adults closely approximated that of the high endemic areas in Central Eastern United States in the Mississippi and Ohio River Valleys.

The author discusses the role of chickens, bats, pigeons and other birds in preparing the soil in order for the fungus to flourish under proper conditions. He then describes the clinical types of histoplasmosis with emphasis on the pulmonary forms. Histoplasmosis mimics tuberculosis and can infiltrate, cavitate, and calcify in a manner which makes it exceedingly difficult or at times impossible to distinguish from tuberculosis, except by skin testing or isolation of the fungus by culture or animal inoculation. Histologic demonstration of the fungus requires special staining procedures.

The drug of choice when treatment is needed in histoplasmosis is amphotericin B, an antibiotic derived from a variety of streptomyces.—*Frank J. Rigos, M.D.*

Silver, M. D., Mason, W. E. H., Robinson, Clayton L., and Blank, F. Pulmonary aspergillosis. *Canad. M. A. J.*, Sept. 8, 1962, *87*, 579–583. (From: Department of Pathology, McGill University, Montreal, Quebec, Canada.)

The authors report 6 cases of pulmonary aspergillosis. This condition is thought to begin with the aspiration of spores and to take one of several courses.

If an aspergilloma results, roentgenograms may show typical findings consisting of a rounded lesion surmounted by a crescentic air cap. This is a mycelial mass situated in a lung cavity. Such lesions remain unchanged for years. Other types of fungus balls, blood clot or necrotic debris in an abscess cavity and a ruptured hydatid cyst may give a similar appearance.

The chronic bronchial form of aspergillosis simulates reinfection tuberculosis, with unilateral or bilateral infiltration of the lung apices often associated with cavitation. Usually there is a chronic cough and repeated hemoptyses.

Pneumonic pulmonary aspergillosis has no distinctive clinical features. It is a more severe form and terminally it may become generalized with abscesses in many organs. Surgical removal of localized disease is the most satisfactory form of treatment. Diagnosis of this mycotic infection requires the close cooperation of the clinic and the laboratory.—*Arthur E. Childe, M.D.*

Supramaniam, J. M. J. The first reported case of broncholithiasis in Singapore. *Singapore M. J.*, June, 1962, *3*, 94–97. (From: Tan Tock Seng Hospital, Singapore, Singapore.)

The author presents an excellent review of the literature regarding broncholithiasis. The first case of broncholithiasis from Singapore is reported. This patient had an obstruction of the right lower lobe bronchus by 12×6×6 mm. broncholith which was removed at bronchoscopy. Two broncholith fragments were coughed up following bronchoscopy. The recovery was uneventful.—*George A. Miller, M.D.*

Braedel, H. U., Haage, H., and Kebekus, H. Erfahrungen mit dem neuen Kontrastmittel "Broncho-Abrodil." (Experiences with the new contrast material broncho-abrodil.) *Radiol. clin.*, 1962, *31*, 101–110. (Address: Dr. H. U. Braedel, Chir. Univ.-Klinik, Röntgen-Abt., Giessen, Germany.)

The new contrast medium broncho-abrodil (Bayer 12 38) was used for 84 bronchographies. This medium is a suspension which is only slightly soluble. The contrast is very good. There is good adhesion to the bronchial walls. It is able to pass through stenotic areas with ease. The speed of its absorption depends on the state of normality of the bronchial mucosa. It disappears from the lung fields much slower than water-soluble media which, however, have other undesirable reactions.—*Hans W. Hefke, M.D.*

Wellington, J. L. The shrapnel awakes: pyopneumothorax and chronic empyema resulting from a foreign body retained for 17 years. *Canad. M. A. J.*, Aug., 1962, *87*, 349–351. (From: The Cardio-Thoracic Unit, Queen's University, Kingston, Ontario, Canada.)

This is a single case report of a patient in whom a pyopneumothorax and encysted empyema developed, following a latent and asymptomatic period of 17 years after a shrapnel injury to the chest. The metallic fragment was lying free in an empyema sac and a lung abscess was found nearby.

In view of the possibility that such a complication

may occur so long after an injury of this nature, the policy of early removal of all strategically placed foreign bodies larger than 1 cm. in diameter is supported.—*F. B. Markunas, M.D.*

Gibel, W., Matthes, Th., and Spode, E. Weitere Untersuchungen über die Anwendbarkeit einer^{198}Au-Kohlesuspension zur Diagnostik pulmonaler Zirkulationsstörungen. (Further investigations with radioactive gold^{198}-carbon suspension for diagnosis of disturbances of the pulmonary circulation.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Aug., 1962, *97*, 186–195. (Address: Dr. W. Gibel, Deutsche Akademie der Wissenschaften zu Berlin-Klinik, Lindenberger Weg 80, Berlin-Buch, Germany.)

After animal experimentation proved intravenous injection of Au^{198}-carbon suspension to be harmless, the same procedure was used in 7 patients with advanced primary or metastatic pulmonary neoplasm. In this method, 200 mg. of carbon and 200 μc of Au^{198} in physiologic saline are injected into an arm vein. The scintillation count is taken ½ to 1 hour after injection. A decrease in pulmonary vascularity is seen as a decrease in the uptake compared with the normal areas of the lung.

This method determines the site and extent of the pulmonary disturbance without giving any indication of the cause. A decreased uptake will be found in pulmonary infarction, chronic pneumonia, neoplasm, atelectasis and emphysema.

Although angiography discloses more details, catheterization is not as well tolerated as the intravenous injection of the radioactive material. The latter procedure offers a rapid and harmless method for the determination of pulmonary disturbances.—*J. Zausner, M.D.*

McMullen, Faber F., Jr., Sutton, William C., Allen, Herbert C., and Hanson, Hugh H. Detection of the small left-to-right intracardiac shunt with methyl iodide I-131. *J. Nuclear Med.*, Sept., 1962, *3*, 367–381. (From: The Department of Nuclear Medicine, Hermann Hospital and Department of Internal Medicine, Cardio-Respiratory Section, Hermann Hospital, Houston, Tex.)

Methyl iodide tagged with I^{131} has been employed by several groups for detection of left-to-right intracardiac shunts. In the test as performed by the authors the patient is first given Lugol's solution to block the thyroid gland. A cardiac catheter is introduced into the right heart and a plastic hood is placed over the patient. The tracer is administered into the oropharynx through a premature infant feeding tube during inspiration from the metal cylinder in which it is prepared. The size of the tracer dose is not stated but would appear to be approximately 20 μc. Methyl iodide content is well below toxic levels. As the tracer is being administered, simultaneous, timed 1 ml. blood samples are withdrawn through the cardiac catheter. Activity in the samples is detected in a scintillation well counter.

Several cases are presented to support the authors' contention that the methyl iodide I^{131} inhalation technique is a sensitive detector of small left-to-right shunts, perhaps more sensitive than the measurement of oxygen gradients or the contrast medium dilution technique.—*Frederick J. Bonte, M.D.*

Wholey, Mark H., Walker, James H., Hartman, John M., and Haskin, John. The application of radioactive gas in the detection and quantification of left-to-right cardiac shunts. *Radiology*, July, 1962, *79*, 51–57. (From: The Departments of Radiology, Medicine, and Cardiovascular Surgery, Charleston Memorial Hospital, Charleston, W. Va.)

The utilization of an inert nonradioactive gas for detecting left to right cardiac shunts has been established clinically and the use of nitrous oxide has been shown to be superior to conventional oximetry. Unfortunately, nitrous oxide determination is a difficult laboratory procedure. Therefore, the introduction of radioactive gasses to detect left to right cardiac shunts by inhalation and simultaneous right heart sampling has been a valuable addition to cardiac diagnosis. The principle of the test is based on the natural pathway of the gas after inhalation. In the presence of a left to right cardiac shunt, blood samples from the right chambers of the heart and pulmonary artery will demonstrate a marked early appearance of radioactivity after inhalation, with the position of the catheter qualitatively localizing the shunt site. The method has been shown to be diagnostically superior to oximetry and of comparable accuracy to nitrous oxide determinations.

The authors' experience has consisted of the evaluation of krypton 85, xenon 133 and methyl iodide 131. The advantages and disadvantages of each are discussed. Because of the ease of production, ready availability, and favorable physical characteristics, methyl iodide 131 was found ideally suited to their facilities. The method of producing methyl iodide 131 is described as is the method of administration to the patient. Another attractive feature of the test is that it can be performed with no specialized equipment other than a well scintillation counter.

A total of 100 patients were evaluated with methyl iodide 131 during either cardiac catheterization or selective angiocardiography in patients with

suspected left to right shunts. There were 45 interatrial septal defects, 22 interventricular septal defects, 8 patent ducti, and 2 total anomalous venous connections. In 23 no evidence of a shunt was obtained. Of the 77 patients with evidence of a left to right shunt, the methyl iodide 131 accurately localized the defect in 72 instances for an over-all accuracy of 93 per cent. This compares favorably with an accuracy of 84 per cent for oximetry and 80 per cent for combined clinical and electrocardiographic findings. Typical curves for qualitative localization are presented. Accurate quantitative data are unreliable for the present because of absorption of methyl iodide 131 by the tracheal epithelium.

The authors conclude that the test is accurate and simple in qualitative localization of left to right shunts. Metabolic changes will not influence the results and the test can be performed in conjunction with oximetry or during angiocardiography with or without general anesthesia. It is possible that small shunts overlooked by conventional oximetry are more easily localized by the methyl iodide 131 test.—*E. B. Best, M.D.*

Abdomen

Meireles, José de Souza, Montenegro, Mario Rubens, Zaterka, Schlioma, Bettarello, Agostinho, and Pontes, José Fernandes. Gastric ulcer cicatrization: a comparison of roentgenologic and histologic data. *Am. J. Digest. Dis.*, July, 1962, *7*, 661–671. (Address: Dr. J. de Souza Meireles, Scripps Clinic and Research Foundation, 476 Prospect Street, La Jolla, Calif.)

Ulcerated gastric cancer and peptic ulcer may be differentiated when standard modern clinical procedures are employed. There are, however, cases of gastric cancer that, clinically and roentgenologically, behave like gastric ulcers.

The therapeutic test is considered to be the only efficient method in this differentiation. Reports of patients are mentioned whose gastric ulceration healed after treatment but whose lesion later proved to be malignant.

It is said that the scar is not a "healthy and solid tissue." The appearance of healing observed on roentgenograms is the result of improvement of the local conditions around the ulcer related to decrease in inflammation. More serious objection to the therapeutic test comes, however, from claims that the scar may cover or mask a neoplastic growth.

Proof is lacking that roentgenologic healing corresponds to a scar lined by almost normal mucosa.

Study of 6 cases, described in detail, permits the statement that the disappearance after treatment of the roentgenologic signs of a gastric ulcer correlates fairly well with the histologic healing of the lesion.

Grossly, the scar appears as a small, round, depressed area in the mucosa, which in cross section reveals an obliteration of the components of the wall by fibrous tissue.

Histologically, the scar in the wall is made up of fibrous tissue. It usually obliterates all the components of the wall except for the regenerated mucosa. The scar is composed of mature connective tissue, with few blood vessels and a very scanty inflammatory infiltrate.

The muscularis mucosae is interrupted. A large portion of the scar is covered by fairly normal muscularis mucosae that loses the normal pattern only in the center, where there is a partial or complete obliteration of its bundles by fibrous fascicles.

The mucosa that covers the scar is composed of loose connective tissue containing glands and lined by surface epithelium. Inflammatory cells are present in the stroma. The pattern of the glands is altered, and they are irregular in shape, being usually of the pyloric type; some show the appearance described as intestinal metaplasia. Typical gastric glands like the ones found in the gastric body were not found.

All were patients in whom something went wrong in the process of healing, as a result of which they underwent surgery. In some, the symptoms of ulcer had recurred for many years; in others, at operation some roentgen evidence of ulceration was still present. In addition, the stomachs of these patients were examined shortly after the roentgenologic signs diminished or disappeared.

In the large numbers of patients in whom the roentgen signs of ulceration disappear completely and rapidly after treatment, the process of healing is much more complete, especially after a longer period of time.

The possibility that healing and epithelization may occur in a malignant lesion was not observed in these cases. Although not entirely normal, the elements present in the scar had all the components of the gastric mucosa. It is difficult to conceive of these elements growing over a carcinoma.

The authors do not think it likely that malignant tissue is capable of replacing completely an ulceration to the point of rendering it invisible on the roentgenogram. Even if the neoplasm behaves in this peculiar manner, the rigidity of the wall will help to identify malignancy.

It is the opinion of the authors that the only reliable clinical criterion assuring the benign nature of an ulcerated gastric lesion is its roentgenologic and/or gastroscopic healing after therapy.—*Stephen N. Tager, M.D.*

Bishop, Harry C., and Hope, John W. Pyloric stenosis: postoperative roentgen studies and their clinical significance. *J. Pediat.*, Jan., 1962, *60*, 62–68. (Address: The Children's Hospital of Philadelphia, 1740 Bainbridge Street, Philadelphia 46, Penn.)

Usually infants who have undergone pyloromyotomy have an uneventful postoperative course. On occasion there will be persistent vomiting suggesting that the surgical procedure was inadequate. For these reasons postoperative roentgen studies were carried out on 20 infants selected at random following a pyloromyotomy.

These studies were done at varying times. The earliest was on the second postoperative day and the latest, 6 months. Six of the infants had repeat examinations. The usual technique of examination and the findings are described.

All 20 babies showed postoperatively, a persistent pyloric canal abnormality of variable degree. These ranged from persistent narrowing and elongation of the entire pyloric canal to a persistence of the indentation into the duodenum by the hypertrophic muscle and referred to as the "umbrella sign."

Studies a few days after operation demonstrated, in most cases, the same findings as found preoperatively. However, gastric emptying time was improved. As time passed, the pyloric canal gradually shortened and widened. The invagination into the duodenal bulb usually persisted for several months. Thus, there was no accurate correlation between the clinical improvement and the roentgen picture following pyloromyotomy.

The decision to perform a second pyloromyotomy should not be based on the roentgen findings alone.—*John L. Gwinn, M.D.*

McCollough, W. Eugene. Foreign body in the stomach of a premature infant. *J. Pediat.*, Feb., 1962, *60*, 277–279. (Address: San Bernardino County Charity Hospital, San Bernardino, Calif.)

A case is reported of a premature infant who, at 1 week of age, developed pneumonia and was treated with antibiotics and corticosteroids. On the eleventh day of life, a barium meal was given because of persistent coffee-ground vomitus. A roentgenologic diagnosis of gastric ulcer and hiatal hernia was made. This was treated symptomatically as in the adult.

A follow-up barium meal was administered on the 23rd day and did not show either the hiatal hernia or ulcer, but a large filling defect was noted within the stomach. This was not attached to the gastric walls. Another study, 24 hours later, revealed the same defect.

The infant was given small frequent feedings until 12 weeks of age at which time normal feedings were tolerated. A study at 50 weeks failed to demonstrate any abnormality of the stomach. It is postulated that the filling defect had been mucus and later had been passed through the gastrointestinal tract.—*John L. Gwinn, M.D.*

Manecke, H., and Schmidt, F. W. Die Magen-Darm-Passage mit Karion. (The effect of Karion on gastrointestinal passage.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Aug., 1962, *97*, 142–146. (Address: Dr. H. Manecke, Med. Univ.-Poliklinik, Robert-Koch-Str. 7a, Marburg/Lahn, Germany.)

The addition of liquid Karion F, an odorless, harmless and sweet tasting solution, to the barium meal affords a rapid visualization of the small bowel without causing any physiologic changes in the mucosal pattern. In 80 per cent of the cases with 10 cc. Karion, satisfactory studies of the small bowel can be made. After 1 hour, the mixture has reached the mid ileum. Another 20 cc. Karion is given at this time to maintain a continuous column of contrast material from the stomach to the mid descending colon.

This method is particularly valuable when the examination must be completed within the morning hours. The authors make no mention of any attempt to evaluate the opacified portion of the large bowel.—*J. Zausner, M.D.*

Spiro, H. M. Stomach damage from aspirin, steroids and antimetabolites. *Am. J. Digest. Dis.*, Aug., 1962, *7*, 733–743. (From: Yale University School of Medicine, New Haven, Conn.)

Three different mechanisms by which drugs can cause stomach damage are reviewed. Three representative drugs were chosen as illustrations. Aspirin directly injures the gastric mucosa without changing the gastric secretion; steroids do increase gastric secretion; and 5-fluorouracil is typical of drugs which inhibit mitoses.

Single .6 gm. doses of aspirin did not change human gastric secretion. However, 1.5 to 3 gm. of aspirin daily for an unspecified period caused occult blood in the stool of 75 to 80 per cent of patients. The blood loss was thought to be on the order of 5 cc. daily. The addition of buffers made no difference in the degree or incidence of bleeding. In a study of 96 patients who experienced gastrointestinal bleeding, 44 per cent negative gastrointestinal examinations were reported of those who had taken aspirin immediately before each episode, while only 25 per cent of the group that had not taken aspirin had negative gastrointestinal examinations. A more striking statistic is that 56 per cent of patients who had gastrointestinal bleeding without evidence of ulceration on roentgen examination had a history of aspirin intake just prior to the hemorrhage. Various studies have shown gastroscopic evidence of hyperemia and hemorrhage around aspirin tablets in the stomach. Erosion of gastric mucosa has been reported in gastrectomy specimens underlying the undissolved aspirin particles. The effect of aspirin appears to be

that of generalized gastritis with superficial erosions of the gastric mucosa.

Short term administration of steroids will not alter gastric secretion, whereas extended use will lead to an increase in pepsin concentration, total pepsin, and free acid. Routine gastrointestinal studies of 117 patients on steroids for rheumatoid arthritis demonstrated peptic ulceration in 31 per cent. This contrasts with the much less frequent recognition of steroid ulcer in patients with chronic ulcerative colitis or skin disease. The relationship of aspirin and steroids in patients with rheumatoid arthritis may account for the increaseed incidence of peptic ulcer by steroid induced enlargement and extension of superficial erosions which were caused by aspirin.

The 5-fluorouracil has a more general effect on the gastrointestinal tract, although the stomach is apparently spared. Nausea and vomiting, dysphagia, and diarrhea attest to the diffuse injury.—*Burton Silbert, M.D.*

LEVENE, GEORGE, and SCHEFF, SAUL. The clinical significance of duodenal diverticula. *Am. J. Digest. Dis.*, Oct., 1962, *7*, 877–885. (Address: Dr. G. Levene, Massachusetts Memorial Hospitals, 750 Harrison Avenue, Boston 18, Mass.)

The authors discuss the development and significance of duodenal diverticula. Although they are usually without significance, it is pointed out that they can cause rather severe symptoms including gastrointestinal bleeding and pain. The symptoms may be suggestive of duodenal ulcer. A diverticulum may produce symptoms when it retains food or other foreign body. It may contain functioning aberrant glandular tissue and may be the site of ulceration, perforation, or gangrene. These possibilities must be carefully considered in the examination of the patient who has a duodenal diverticulum and symptoms which are not otherwise explained.—*George L. Sackett, Jr., M.D.*

SIMON, MORRIS, and LERNER, MAURICE A. Duodenal compression by the mesenteric root in acute pancreatitis and inflammatory conditions of the bowel. *Radiology*, July, 1962, *79*, 75–81. (Address: Beth Israel Hospital, 330 Brookline Avenue, Boston 15, Mass.)

Anatomically, the third part of the duodenum crosses the aorta just distal to the origin of the superior mesenteric artery which is contained in the root of the mesentery. In chronic arteriomesenteric duodenal occlusion, intermittent duodenal compression has been shown to be due to a decrease in the angle between the mesenteric root and the aorta, associated with congenital abnormalities of the mesentery, rapid weight loss, exaggerated lumbar lordosis, or large pelvic prolapse or hernias.

The authors describe a similar compression of the third part of the duodenum occurring as an acute transient phenomenon, secondary to intra-abdominal disease. Case reports are presented in which duodenal compression was seen in acute pancreatitis, an acute exacerbation of regional ileitis, infarction of the jejunum secondary to mesenteric venous thrombosis, and acute duodenal ulcer. In these conditions, the compression occurred only during a particular clinical episode and was not relieved by a change in posture to widen the angle, as may occur in the chronic form.

In the authors' acute cases, thickening of the mesenteric root due to inflammation, hemorrhage, or fat necrosis and inflammatory swelling of the bowel wall produced the same mechanical effect as a decrease in the angle between the mesenteric root and the aorta. The detection of minor degrees of compression is of importance, therefore, in the investigation of obscure acute abdominal conditions. In the absence of duodenal ulcer, enteritis or colitis, the diagnosis of acute pancreatitis should be considered and further investigated.

The authors propose that this phenomenon, when encountered, be referred to simply as duodenal compression by the mesenteric root, either acute or chronic, and qualified, if possible, by the specific cause.—*Ralph Bowman, M.D.*

FELCI, U. La duodenografia ipotonica nelle affezioni pancreatico-vateriane. (Hypotonic duodenography in pancreatic vaterian lesions.) *Radiol. med.*, May, 1962, *48*, 431–447. (Address: Piazza Gorini, 22, Milano, Italy.)

Hypotonic duodenography has been performed with the intent of visualizing alterations of the duodenal wall secondary to lesions of the pancreatic head and of the vaterian area at an early stage.

The technique employed by the author is the one suggested by Liotta in 1956. The duodenal tube is introduced and the position of its tip in the duodenal bulb or in the second portion of the duodenum is controlled roentgenoscopically. Fifteen minutes after the intramuscular injection of a synthetic anticholinergic (antrenyl-Ciba), 10 ml. of diluted viscous xylocaine is instilled through the tube. The local anesthesia so obtained potentiates the hypotonic effect of the anticholinergic substance and facilitates movement of the tube. Ten minutes later, with the patient in a supine position and under fluoroscopic control, a barium suspension is introduced. A double contrast study is obtained following aspiration of the barium and insufflation of air.

Hypotonic duodenography permits a selective, detailed, roentgenographic study of the second and third portions of the duodenum. Used in conjunction with conventional means of investigation, it throws

light on diseases of the duodenum, pancreas and papilla of Vater.—*Anthony A. Blasi, M.D.*

Liszka, Gy., and Székely, Á. Pharmakoradiologische Untersuchungen von Duodenalgeschwüren. (Pharmaco-radiologic examination of duodenal ulcers). *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Aug., 1962, *97*, 169–173. (Address: Dr. Gy. Liszka, János-Krankenhaus, Budapest, Hungary.)

The pharmacologic action of 12 drugs was studied in 110 patients with known or suspected duodenal ulcers. Morphine, 5–10 mg., and atropine, 1.0 mg., gave the best results in patients whose duodenal ulcer could not be satisfactorily visualized because of spasticity and hypertonicity of the stomach combined with irritability of the duodenal bulb. Morphine caused dilatation of the gastric antrum, improved patency of the pyloric canal, increased gastric peristalsis and produced excellent filling of the duodenal bulb in 23 of 25 cases without any ill effects; 2 patients experienced mild attacks of vomiting. Atropine carries the risk of producing an exacerbation of a pre-existing glaucoma but dryness of the mouth and cardiac palpitation are not serious. Gastric peristalsis and tonicity are increased immediately after subcutaneous injection of atropine but subside within 10 to 15 minutes, therefore study should be made promptly after the injection.

Prostigmin is unsatisfactory because it produces increased gastric secretion which dilutes the contrast material; in 3 of 5 cases, hyperperistalsis prevented adequate filling of the duodenal bulb, so that previously demonstrable ulcers were not visualized. Oxyphenonium-bromide (1.0 mg. I.M.) is similar to atropine and produced excellent filling of the duodenal bulb in 15 to 20 minutes after the injection. Adrenalin is not desirable because of the dizziness and cardiac palpitation which follow its injection. Guanethidine (a sympatholytic drug) causes a drop in blood pressure and does not produce satisfactory filling of the duodenal bulb. A variety of sympatholytic drugs caused hypotensive states and are therefore not recommended. Spasmolytic agents, such as aminopromazine and papaverine, produced relief of pre-existing spasms without any disturbing side reactions.—*J. Zausner, M.D.*

Vest, Bruce, and Margulis, Alexander R. The roentgen diagnosis of postoperative ileus-obstruction. *Surg., Gynec. & Obst.*, Oct., 1962, *115*, 421–427. (From: The Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Mo.)

Many patients, following operations, develop a confusing clinical and roentgenologic picture which has some features of both mechanical obstruction and adynamic ileus.

Differentation between these is important in proper handling of the patient.

The authors evaluated a method of study of these cases using an oral, water soluble contrast material (30 to 40 per cent solution of sodium diatrizoate, hypaque).

First a group of patients, who did not develop complications postoperatively, were studied to determine intestinal transit time. The usual stomach to cecum time in this group was found to be 2 to 3 hours, with all cases under 4 hours.

These were compared with patients who developed the postoperative ileus-obstruction clinical picture.

The method used was to give 100 cc. of the 30 per cent solution orally (40 per cent in cases with a nasogastric tube in place). The patient was then placed on the right side to help gastric emptying. Roentgenograms of the abdomen were made at 1, 1½, 2, 3, and 4 hours after administration of this solution. Occasionally even more delayed roentgenograms were helpful. One upright roentgenogram should be obtained to study air fluid levels.

This procedure was found to be of definite value in distinguishing between the cases of mechanical obstruction and those with adynamic ileus. It may be used in instances when barium sulfate solution might be contraindicated.

The authors report several interesting cases and conclude that:

Absence of obstruction is shown by a stomach-cecum transit time of a water soluble contrast material of less than 4 hours.

A stationary column of contrast material for a period of 3 to 4 hours indicates a complete obstruction of the small intestine.

A slowly moving column with transit time of more than 4 hours and with disparity in the width of the small intestinal loop suggests incomplete obstruction and indicates need for further evaluation.

The correct diagnosis as to whether or not mechanical obstruction is present, is of great importance in the postoperative patient and is facilitated by a water soluble contrast study of the tract.—*George L. Sackett, Jr., M.D.*

Larson, Duane L., Karzel, Ronald, and Cameron, John. Intestinal intubation with the aid of a magnetic tube. *Surg., Gynec. & Obst.*, Oct., 1962, *115*, 503–504. (From: The Departments of Surgery and Radiology, University Hospitals, Madison, Wis.)

Decompression of the obstructed, distended small intestine by intubation, though effective, is often beset with difficulty. Not uncommonly, the tube tip will not enter the pylorus and duodenum. Delay and frustration in the execution of this procedure are lessened if the tube tip can be "steered" and its

passage facilitated by external means. This is achieved through the use of an electromagnet if a small permanent magnet is first placed in the tube tip.

Before intubation, the polarity of the small magnet is checked to be certain that the electromagnetic field will attract and not repulse the tube tip. The tube is then passed to the stomach and observed by fluoroscope. When the tube tip is in the distal antrum, the electromagnet is applied at the right midaxillary line near the costal margin and the rheostat adjusted for optimal control of the tip. Then, as the tube is manually advanced through the nose, the tip is magnetically directed and pulled through the pylorus. Once it is in the duodenum, the patient is turned toward his left side and the electromagnet applied to the posterior axillary line to effect passage downward and through the second portion of the duodenum, etc. If folds prevent free passage through the stomach, the tube can be diverted magnetically and if difficulty persists, the instillation of saline solution will separate the gastric walls and facilitate passage.

Occasionally, the decompression of small bowel is found to be necessary during abdominal surgery. This can be effected by trocar and suction, but may lead to peritoneal contamination. The hazard may be averted if the magnetic tube is employed and passed through the duodenum as in nonoperative intubation. Then, the electromagnet can be placed over the abdomen so that the tube tip stands vertically where it can be grasped and easily and quickly advanced by the surgeon. The techniques described have been used repeatedly without complication.—*Jack Reynolds, M.D.*

Willox, S. W. Intestinal obstruction caused by polycystic disease of the kidneys. *Brit. J. Urol.*, Sept., 1962, *34*, 267–269. (From: Leith Hospital, Edinburgh, Scotland.)

Intestinal obstructive symptoms may be caused by polycystic kidneys in a variety of ways. Some degree of paralytic ileus, giving the distended silent abdomen, is not an uncommon complication in patients dying from uremia. Mechanical intestinal obstruction from polycystic disease is, however, a rare complication.

The author reports a case in which there was a bilateral polycystic kidney with a very large left kidney which was non-functioning and which pressed upon the large bowel over the anterior aspect of the sacrum. The left kidney was excised and the patient was allowed to go home one month after operation having made an uneventful recovery. The blood urea nitrogen was 37 mg. per 100 ml. Two months later she was back at work. Unfortunately the right polycystic kidney has been steadily enlarging during the past year with the blood urea nitrogen at the last examination being 67 mg. per 100 ml.

The author also discusses briefly 2 other cases reported in the literature in which there was apparently some degree of mechanical intestinal obstruction present.

It is concluded that the size of the kidney with some secondary infection plays a part in producing mechanical obstruction of the large bowel.—*Peter C. Truog, M.D.*

Khilnani, Mansho T., Wolf, Bernard S., and Finkel, Martin. Roentgen features of carcinoma of the gallbladder on barium-meal examination. *Radiology*, Aug., 1962, *79*, 264–273. (From: The Department of Radiology, Mount Sinai Hospital, New York, N.Y.)

Carcinoma of the gallbladder comprises about 4.5 per cent of all carcinomas discovered on necropsy. A correct preoperative diagnosis, however, is seldom established unless jaundice is present and a solid mass in the right upper quadrant can be identified and related to the gallbladder. In most instances a clinical diagnosis of obstructive jaundice due to common duct stones or carcinoma of the pancreas is made. Barium meal examinations done in these jaundiced patients usually show positive findings but are interpreted most commonly as being due to carcinoma of the pancreas. Because of this the authors reviewed 16 cases of carcinoma of the gallbladder in which adequate barium meal examinations had been done and in which the films were available for study.

Characteristically, the portion of the duodenum maximally affected by carcinoma of the gallbladder is the segment of the first portion of the duodenum between the apex of the bulb and the superior flexure, which is the beginning of the second part or descending duodenum. The changes seen here consist of extrinsic pressure and neoplastic infiltration. This segment is usually elongated, compressed and infiltrated on its superior and lateral or anterior aspects. The duodenal bulb frequently has a peaked configuration with flattening on its lateral aspect. The elongated postapical portion of the duodenum is displaced somewhat medially so that it lies directly behind the bulb. The involved infiltrated mucosal folds are often distorted and rigid and there is a fixed relationship between the bulb and postapical segment, despite changes in position of the patient.

These roentgen findings are best demonstrated in the right oblique or lateral position, and rarely in the posteroanterior projection with the patient prone or erect. Differential diagnosis must include pressure defects due to a normal or enlarged gallbladder, carcinoma of the head of the pancreas, dilatation of the common duct, and masses in the liver. The changes seen with a normal or enlarged gallbladder are changeable with different degrees of duodenal filling or change in position of the patient. The pressure defect is more discrete and arcuate and there are

no distorted, fixed mucosal folds. The defects and mucosal changes from carcinoma of the head of the pancreas are found on the medial aspect of the duodenal sweep and duodenal bulb. Dilatation of the common duct is usually present with carcinoma of the head of the pancreas and when present is evident roentgenologically by a typical tubular defect on the medial aspect of the first portion of the duodenum. A mass in the liver may compress and elongate the postapical duodenum but rarely infiltrates or becomes fixed to the duodenum and is usually located more anteriorly, in front of the duodenal bulb and antrum.—*Donald N. Dysart, M.D.*

Cugini, A., and Sosso, A. Colangiografia retrograda da reflusso duodeno-biliare transpapillare. (Retrograde cholangiography with transpapillary duodeno-biliary reflux.) *Ann. radiol. diag.*, 1962, *35*, 163–172. (From: Istituto di Radiologia dell'Università di Torino, Turin, Italy.)

The authors report a case in which during an upper gastrointestinal tract examination, there was a reflux of barium into the biliary tree in a patient who had had a cholecystectomy several years previously.

The patient, a 65 year old female was suffering from painful dyspepsia and vomiting. Eight years before she had a diagnosis made of chronic gallbladder disease with stone. Because of her poor general condition and severe jaundice, a cholecystotomy was done after which there was a gradual improvement of her condition. Two months later a cholecystectomy was performed and at that time adhesions and inflammatory tissue were seen about the common duct. No stones were found within the common duct nor any neoplastic growths. During this upper gastrointestinal series nothing remarkable was observed until the second portion of the duodenum was filled with barium, when there was rapid filling of the entire bilary tree with barium. The common duct and radicals were distended with numerous filling defects seen within the lumen which were believed to be due to retained reflux food. Barium within the biliary tract was observed as long as 8 hours after administration of the barium meal. The size of the common duct remained constant.

The authors' opinion is that this case represents a true transpapillary duodeno-biliary reflux due to incompetence of the sphincter of Oddi as a result of chronic inflammation. Other more common causes, such as duodeno-biliary fistula are discussed in the article. Also discussed are functional changes which may influence the sphincter of Oddi and pressure changes within the lumen of the duodenum and within the biliary tree.

There was no follow-up on the patient, nor is it stated whether subsequent examinations of the upper gastrointestinal tract were made to see if this filling of the biliary tract could be repeated.

Transpapillary biliary filling of the biliary tract is certainly a very rare phenomenon.—*Peter E. Russo, M.D.*

Longin, F., and Marx, I. Vergleichende Untersuchung mit Osbil und Orabilex, zwei neuen oralen Gallenkontrastmitteln, durch Erprobung am gleichen Patienten. (Comparison of two new oral contrast media for cholecystography, osbil and orabilex, by using them with the same patients.) *Röntgen Blätter*, Aug., 1962, *15*, 261–267. (Address: Dr. Franz Longin, Med. Univ.-Poliklinik, Klinikstrasse 8, Würzburg, Germany.)

Osbil and orabilex, two new cholecystographic media were used on 52 patients, each one on the same patient with intervals of about 5 days. The results obtained with orabilex were more satisfactory.

(The reviewer is not aware that osbil is available in the United States and its chemical name is not given.)—*Hans W. Hefke, M.D.*

Felci, U. Il "Segno del Dotto" nella diagnosi radiologica di pancreas aberrante. (The "duct sign" in the radiologic diagnosis of aberrant pancreas.) *Ann. radiol. diag.*, 1962, *35*, 249–257. (From: Istituto di Radiologia dell'Università di Milano, Milan, Italy.)

Three cases of aberrant pancreas are presented by the author. The first case was verified by surgical intervention. The other 2 cases were followed and examined for long periods of time. The third case was checked by gastroscopy.

The roentgenologic signs which were first described by Kjellmann consist of a smooth filling defect with an umbilicated area and filling of a duct with a blunted blind portion. This duct shows changes in size as it fills and empties. This picture conforms to a glandular intramural growth with excretory duct and open lumen which varies in appearance in different projections.—*Peter E. Russo, M.D.*

Ozonoff, M. B. Roentgenologic demonstration of intra-hepatic hematoma following liver biopsy: report of a case. *Am. J. Digest. Dis.*, Sept., 1962, *7*, 844–849. (From: The Department of Radiology, San Francisco General Hospital, San Francisco, Calif.)

The author reports the case of a woman 78 years of age who, following liver biopsy, developed an ill-defined tender mass in the right abdomen which could not be separated from the liver by palpation. As she was not a good operative risk thorotrast was injected intravenously to opacify her liver. This revealed in the right superior portion of the liver a radiolucent area which was subsequently shown by needle aspiration and laparotomy to be a hematoma.

Hematomas occasionally occur not only after liver biopsy but also coincident with long-term anticoagulant therapy. He believes that the use of this radioactive substance is justified in elderly patients who are poor operative candidates when an intra-hepatic hematoma is suspected.—*Arthur E. Childe, M.D.*

Gynecology and Obstetrics

Lenz, W., and Knapp, K. Foetal malformations due to thalidomide. *German Med. Monthly*, Aug., 1962, *7*, 253–258. (From: The Paediatric Department, University of Hamburg, Hamburg, Germany.)

The authors reviewed 129 cases of children born with the typical fetal malformations associated with thalidomide, with or without a definite history of ingestion. A second group studied was 203 cases with fetal malformations following a definite maternal history of ingestion.

The incidence of certain malformations was shown to have increased markedly since thalidomide became widely available. The evidence for the etiologic agent being the drug was again found to be fairly conclusive. The critical period for production of malformations is thought to be ingestion of the drug from the 37th to the 50th day after conception.

The best known malformations are the major deformities of the limbs. Lesser bony and soft tissue abnormalities were noted, however, such as hypoplasia of the thumb or thenar eminence, syndactilism involving the thumb and first finger and triphalangia of the thumb. Of particular interest were 30 patients with cardiac anomalies, 12 with duodenal stenosis or atresia, 7 with anal atresia and 4 with spastic pyloric hypertrophy. Most of these occurred in association with the malformation of the limbs but some did occur independently also.

This latter group of anomalies has not been stressed in previous publications. If observation of these malformations is followed by close questioning, more cases of fetal abnormalities due to thalidomide ingestion may be recognized.—*Barry E. Gerald, M.D.*

Gillis, Leon. Thalidomide babies: management of limb defects. *Brit. M. J.*, Sept., 1962, *2*, 646–647. (Address: Consultant Orthopaedic Surgeon, Queen Mary's Hospital, Roehampton, S.W. 15, England.)

There is now a clearly defined clinical syndrome resulting from thalidomide administration during the early weeks of pregnancy. It consists of facial hemangiomata, saddle nose, microtia, coloboma, and amelia or phocomelia. Defects of the cardiovascular, urogenital, and intestinal systems are common but there is rarely mental retardation.

Management consists of conservative correction of deformities, surgery to salvage badly deformed limbs, amputation and the use of prostheses. In the interest of mental and emotional adjustment prostheses should be fitted as early as possible, often before the child is one year old, and always during the preschool period. Early fitting is especially important in defects of an upper limb where acquired movement patterns are of prime concern. Children adjust themselves admirably and take special delight in overcoming difficulties and learning new maneuvers with artificial hands. Externally powered prostheses are becoming refined, especially those using electric motors and compressed gases. When amputations are necessary, disarticulation through the knee or elbow joints is preferable because of better probable adaptation to prostheses.—*Arch H. Hall, M.D.*

Ward, S. P. Thalidomide and congenital abnormalities. *Brit. M. J.*, Sept., 1962, *2*, 646–647. (From: Department of Clinical Pathology, Staffordshire General Infirmary, Stafford, England.)

A case report of typical thalidomide induced fetal deformity is given. The drug was administered to the mother for 2 months prior to conception and for only 3 weeks after the pregnancy began. It is known that limb buds do not start to form until the sixth to seventh week of intrauterine life and therefore in this instance the time at which the agent was administered did not coincide with the time at which it exerted its deleterious effects.

It is suggested that since the use of the teratogen began before pregnancy this might have been a factor in achieving a sufficient accumulation by the critical period.—*Arch H. Hall, M.D.*

Coodin, Fischel J., Uchida, Irene A., and Murphy, Claude H. Phocomelia: report of three cases. *Canad. M. A. J.*, Oct., 1962, *87*, 735–739. (From: Department of Pediatrics, University of Manitoba, and the Department of Medical Genetics, Clinical Investigation and Research Unit, Children's Hospital, Winnipeg, Manitoba, Canada.)

Three cases of phocomelia observed in western Canada in a one year period are reported in detail. In only one was there any possibility of thalidomide being the etiologic agent. The authors discuss other possible factors in production of malformations of the newborn. These include rubella, insulin, adrenal steroids, progestogens, folic acid antagonists, heredity, late maternal age, and exposure to irradiation. It may be that other sedatives and antiemetics have teratogenic effects similar to thalidomide but have not yet attracted attention because of their more discrete use.—*Arch H. Hall, M.D.*

Ives, Elizabeth J. Thalidomide and anal abnormalities. *Canad. M. A. J.*, Sept., 1962, *87*, 670–172. (From: The Department of

Pediatrics, University Hospital, Saskatoon, Saskatchewan, Canada.)

Two cases of congenital severe anal stenosis are reported and in both instances the mother had taken thalidomide between the third and eighth weeks of pregnancy. One infant also had minimal hypoplasia of the left ear. There were no associated limb abnormalities.

The anus becomes canalized in the embryo during the eighth and ninth weeks and the external ear is finally formed between the eighth and tenth weeks.

The reported cases of limb deformity secondary to thalidomide occurred when the drug was taken between the 30th and 50th day after the last menstrual period. Therefore, in these cases the critical period for limb formation was passed before the drug was taken.

Without further knowledge as to the action of thalidomide it is impossible to state that this drug was the cause of the abnormalities, but all these cases should be on record.—*Martha Mottram, M.D.*

Kohler, H. G. Congenital transverse defects of limbs and digits: intrauterine amputation. *Arch. Dis. Childhood*, June, 1962, *37*, 263–276. (From: The Department of Pathology, Birmingham Maternity Hospital, Birmingham, England.)

Intrauterine amputation of the extremities is an uncommon and peculiar congenital deformity, characterized by the absence of one or more distal limb portions. The term "amputation" suggests separation, by mechanical force, of a limb already formed rather than a failure of development, but such a view of the pathogenesis of this abnormality is far from universally accepted. It would probably be better to use a neutral term such as "transverse defects", but for the conservatism of medical nomenclature.

Circular grooves around the digits or limbs, and similar soft tissue defects, also known as ring constrictions, are seen usually in association with "intrauterine amputation." Here again, no agreement regarding the etiology exists.

Four cases of transverse defects of limbs or digits are presented in detail, illustrating various aspects of this complex problem.

An "amputation" should be regarded as exogenous if the remaining skeleton shows no developmental or other abnormality that can be causally associated with it. Any abnormality of the osseous system as a whole suggests endogenous causation.

Furthermore, "all bilaterally symmetrical abnormalities and those in which the abnormality consists of an excessive number of parts are endogenous."

The meaning of the terms "endogenous" and "exogenous" may vary from author to author. Kohler suggests that the term "endogenous" in this context should be extended to imply faulty development of the extremities from any causes that are known to produce true congenital malformations in general, either spontaneously or experimentally.

Positive hereditary history is, admittedly, the most unequivocal evidence of the endogenous nature of an "amputation." Other endogenous causes are usually difficult to prove in the individual human case—with the possible exception of virus disease.

Point of teratogenic determination of developmental malformation occurs about the end of the eighth week when the extremities have acquired their gross shape. Endogenous defects, one must assume, originate before that date.

No unanimity is found regarding the gestational age at which exogenous defects arise. The gestational time at which constriction is supposed to occur thus varies within wide limits. The interval between constriction and demarcation is likewise variable.

Dysplasia foetalis is the name given to localized tissue abnormality which leads to circular necrosis and eventual separation of the distal portions of the extremities. It is this type of defective development that results in intrauterine amputation. In these cases sharply defined areas of limb bud tissue are of such inferior quality that only imperfect histogenesis occurs.

Experimental production of transverse defects has been achieved in many ways. *In utero*, the fetal extremities of laboratory animals have been tied with silk; this was followed in due course by typical intrauterine "amputation." The experimenters succeeded in breeding a strain of rabbits with extremital defects as a recessive mendelian character: lesions were preceded by vascular disorders and resulted in demarcation.

The division of transverse extremital defects into those of endogenous and of exogenous causation helps in understanding the problem; the criteria must not be applied too rigidly, and there are cases which cannot be classified.—*Stephen N. Tager, M.D.*

Coleman, Eric N., and MacDonald, Alistair M. Intrauterine myocardial infarction. *Arch. Dis. Childhood*, Aug., 1962, *37*, 444–447. (From: The Royal Hospital for Sick Children, and the Department of Child Health, University of Glasgow, Glasgow, Scotland.)

A case report, autopsy findings, and discussion are presented regarding an infant classified as having cyanotic congenital heart disease with death occurring at 32 days of age. The right ventricular myocardium was replaced by granulation tissue without any evidence of an infectious process.

The opinion of the authors is that the only tenable theory to account for the findings is myocardial infarction as a result of severe ischemia due to occlusion of the right coronary artery at some time

during the course of intrauterine life. Evidence for this conclusion is presented.—*George A. Miller, M.D.*

Genitourinary System

Fletcher, Ronald F., and Frazer, Alastair C. A case of renal failure and osteosclerosis. *Brit. M. J.*, Sept., 1962, *2*, 769–771. (From: The Department of Medical Biochemistry and Pharmacology, University of Birmingham, and the Metabolic Research Unit, Little Bromwich General Hospital, Birmingham, England.)

This is a case report of a 40 year old woman with a generalized osteosclerosis. She had azotemia with a low blood calcium and slightly elevated phosphorus and an elevated creatinine. Intravenous pyelography showed no function. The calcium and phosphorus balances were positive. There was a failure of ACTH production. For the results of extensive chemical analyses see the original report.

Roentgenographic study revealed thickened trabeculae and increased bone opacity throughout most of the skeleton; the changes below the knees and elbows and in the ribs were less marked. A bone biopsy showed dense lamellae and the bone was very hard. There was no osteoclastic resorption. Autopsy also showed large amounts of uncalcified osteoid tissue around the haversian canals. There was a chronic nephritis in one kidney and the other was represented only by a cyst. There was one small normal parathyroid.

In chronic azotemic renal failure there may be skeletal changes manifested as rickets, osteomalacia, osteitis fibrosa and rarely, as in this case, as extensive osteosclerosis, particularly in the spine and skull.—*Martha Mottram, M.D.*

Millard, D. Glyn. Renal siderosis: radiographic manifestations and use of a new diagnostic procedure. *Radiology*, Aug., 1962, *79*, 290–296. (From: Department of Radiology, Massachusetts General Hospital, Boston 14, Mass.)

Renal siderosis is characterized by the deposition of hemosiderin, a form of ferric oxide, in the kidneys. This abnormal deposition occurs in the various hemolytic anemias, congenital and acquired, and the various intravascular hemolytic conditions associated with exogenous toxins and infections, the march and cold hemoglobinuria, and paroxysmal nocturnal hemoglobinuria. When hemosiderin is present in large quantities, the organ in which it is deposited becomes more dense and is more clearly visualized on the plain roentgenogram.

In 2 cases of paroxysmal hemoglobinuria, the author observed abnormally dense renal shadows on plain roentgenograms. The dense kidneys continued to be visible even though their outlines were partially lost in plain roentgenograms of the abdomen taken during respiration. Because of this observation he suggests a new diagnostic procedure, the "motion radiograph," to confirm the observation of too dense kidneys. A plain roentgenogram of the abdomen taken during respiration may also assist in recognition of other "too dense" organs, such as the liver and spleen, that may contain deposits of hemosiderin, thorotrast, or other retained contrast material.—*A. W. Sommer, M.D.*

Chisholm, G. D., and Heard, Brian E. Oxalosis. *Brit. J. Surg.*, July, 1962, *50*, 78–92. (From: The Departments of Surgery and Pathology, Postgraduate Medical School, London, England.)

The authors report 2 cases of oxalosis, with urinary studies of both families; and they review the previous 52 cases reported in the literature.

Oxalosis is a metabolic disorder producing calcium oxalate deposits in the renal and some extrarenal tissues. Progressive urolithiasis and nephrocalcinosis lead to renal failure and death. The majority of patients have presented in childhood or adolescence. However, one of the present patients developed the disease in the third decade and the other in the sixth. The disease is hereditary, either through a dominant or recessive gene.

Increased urinary oxalate levels provide the antemortem diagnosis. Members of an affected individual's family may show hyperoxaluria without other manifestations of the disease. Examination of the kidneys shows small clumps of oxalate crystals on the cut surface although chemical analysis, histochemistry and roentgen ray diffraction may be required for confirmation. The diagnosis was established in one case by renal biopsy.

Roentgenographically bilateral nephrocalcinosis is seen although the changes may not be present for several years after the initial symptoms. The calcifications become more dense as the disease progresses, probably accelerated by the renal failure. The renal outlines may be distorted by a concomitant pyelonephritis. Nephrocalcinosis was not seen in 2 infants who presented with a sudden severe illness.—*Barry E. Gerald, M.D.*

RADIATION THERAPY

Pisani, G., and Nuvolone, U. La telecobaltoterapia del carcinoma gastrico inoperabile. (Telecobalt therapy in inoperable gastric carcinoma.) *Radiobiol., Radioter. e Fis. Med.*, Jan.–Feb., 1962, *17*, 21–29. (From: Istituto Radiologico e Sezione Oncologica dell'Ospedale Maggiore di Novara, Italy.)

Efforts to influence the course of inoperable gastric

carcinoma favorably have been conducted in the past by: (1) utilizing conventional roentgen therapy (Evans and Leucutia, Regelsberger, Pack, Holfelder and others), (2) introducing radioactive sources into the stomach by means of special sounds, and (3) implanting radon seeds or radioactive gold grains directly into the tumor (Levin, Salotti and others).

The authors have treated 88 patients affected with inoperable gastric carcinoma by means of telecobalt therapy. Total tumor doses varied between 2,500 and 6,000 rads delivered daily in doses of 150 to 200 rads.

A detailed statistical evaluation as to survival was not feasible because of the variability in the extension of the disease and in the patients' general condition. The authors state that they have obtained a marked regression of the neoplastic masses in a significant percentage of the cases treated. The symptoms were ameliorated temporarily in most cases. Best results were obtained with tumor doses of 4,000 to 5,000 rads delivered in 3 to 5 weeks.

The authors maintain that telecobalt therapy is worthy of consideration because of its beneficial palliative effects.—*Anthony A. Blasi, M.D.*

Wang, C. C., and Schulz, M. D. The role of radiation therapy in the management of carcinoma of the sigmoid, rectosigmoid, and rectum. *Radiology*, July, 1962, *79*, 1–5. (From: The Department of Radiology, Harvard Medical School and the Department of Radiology, Massachusetts General Hospital, Boston, Mass.)

From 1940 to 1960 inclusive, 111 cases of cancer of the sigmoid, rectosigmoid, and rectum were seen and treated by radiation therapy in the Department of Radiology of the Massachusetts General Hospital. All were histologically verified as adenocarcinoma of varying degrees of malignancy. Recurrences following radical surgery accounted for 86 of this number; 16 had lesions inoperable because of local or distant spread of the disease; 9 had obvious residual cancer in the pelvis following radical or palliative resection.

Tumor doses of 2,000 to 3,000 r were necessary to control pain. Of 76 patients, 63 or 83 per cent obtained satisfactory pain relief from radiation therapy. The response of the tumor mass to radiation was generally not as satisfactory as that obtained for pain. Of 20 patients, 12 had good regression of recurrent masses. Tumor doses of 3,000 to 5,000 r were usually required. Bleeding generally was controlled with lesser amounts of radiation.

In the entire series of 111 patients, there were 58 in whom the disease was potentially curable. Six of these survived 5 or more years without evidence of the disease following radiation therapy, given in doses of 3,500 to 5,000 r or more, supervoltage, at the rate of 1,000 r per week. Dosage of this magnitude can not be delivered satisfactorily other than by the use of supervoltage radiation without producing undue damage to the skin overlying the sacrum or in the perineum. Repetition of palliative irradiation should be avoided if a vigorous course of therapy was given at the first attempt.—*A. W. Sommer, M.D.*

Dargeon, Harold W. Neuroblastoma. *J. Pediat.*, Sept., 1962, *61*, 456–471. (From: The Departments of Pediatrics and Surgery, the Radiotherapy and Chemotherapy Services and the Children's Tumor Registry, Memorial Hospital for Cancer and Allied Diseases, New York, N. Y.)

This is a comprehensive article on neuroblastoma citing its high incidence in children and the concern by pediatricians, pathologists, radiologists and surgeons. Its natural history is only partially understood, making prognosis and appraisal of therapy difficult and perhaps fallacious. Management of this cancer, as with other types of childhood cancer, requires the integrated efforts of several physicians rather than of a single individual. Eradication of the disease and cure by means of surgery, irradiation and chemotherapy are discussed. Photographs, roentgenographic reproductions and tables accompany the article.—*F. B. Markunas, M.D.*

Howes, Patricia, and Osborn, S. B. Reducing radiation hazards in the radium wards. *Brit. M. J.*, Aug., 1962, *2*, 448–451. (From: University College Hospital, London, England.)

Substantial radiation doses may be received by nursing personnel, particularly in gynecologic radium cases. Only on rare occasions did any member of the nursing staff receive as much as 300 mr in a week but it is still desirable to decrease the dose as much as possible.

To reduce the amount of radiation received by the nurses, the following steps were taken: (a) When practical, anesthetics were used which resulted in a short postoperative recovery time; (b) roentgenographic localization was done with a portable machine; (c) a mobile lead screen was used to protect the nurse from thigh to thorax during bedside nursing procedures. The screen was 1 foot high, 3 feet long and was 2 inches thick in the center, but only $\frac{3}{4}$ inch thick at the margins; (d) nurses were instructed regarding the importance of speed when they were close to the patient and were cautioned to remain at the bedside only for essential nursing procedures; (e) the collecting bottle for continuous bladder drainage was not emptied more than twice daily; (f) the patient being treated with radium was placed as far as was practical from the nursing station and not near a patient who required a large amount of nursing attention; (g) when food had to be cut, it was done before the meal was served; (h) when possible, a daily blanket bath by the nurse was omitted while

the radium was in place; and (i) since the radiation dose is highest at the side of the patient and is lower at the head than at the foot, an attempt was made to arrange the bed so that the nurse would approach the patient's head. Measurements indicated that this was an effective procedure.

The above steps reduced the radiation received by the nurse to 30 per cent of its previous level, with the same efficiency in the nursing care.—*J. L. Williams, M.D.*

Fleming, William H., Szakacs, Jeno E., and King, E. Richard. The effect of gamma radiation on the fibrinolytic system of dog lung and its modification by certain drugs: relationship to radiation pneumonitis and hyaline membrane formation in lung. *J. Nuclear Med.*, Sept., 1962, *3*, 341–351. (From: The Radioisotope Laboratory and Radiation Exposure Evaluation Laboratory, U. S. Naval Hospital, National Naval Medical Center, Bethesda, Md.)

The radiation reaction of human lung is characterized by edema, fibrosis, diminished inflammatory response, hyalinization of arterial walls and alveolar membrane formation. In animals hyaline membrane formation is less striking than in humans; however, there is an association in man and dog between total body gamma radiation, hyaline membrane of lung and diminished plasminogen activator. There is also a pathologic similarity between radiation hyaline membrane of lung and neonatal hyaline membrane disease. Defects in lung fibrinolytic activity in children with neonatal hyaline membrane may lead to fibrin formation and hyaline membrane formation.

The lung plasminogen activator normally acts on circulating plasminogen which in turn gives plasmin. This acts on fibrin deposits which are split and then removed or absorbed. When the lung plasminogen activator has been altered by irradiation or when a defect in lung fibrinolytic activity occurs such as in neonatal hyaline membrane disease, the circulating plasminogen remains unchanged. No plasmin is formed. Fibrin deposits take place and following polymerization, hyaline membrane is formed.

The authors proved that radiation pneumonitis is associated with defective lung plasminogen activation. This defect appears by the end of the first postradiation week in dog lungs which have been exposed to 1,500 to 2,000 rads Co^{60} gamma radiation. With the lung's fibrinolytic system thus paralyzed, fibrin deposits persist leading to hyaline membrane formation and ultimately fibrosis of the lung.

Cortisone and heparin, in the doses used, failed to protect or potentiate the effects of Co^{60} gamma radiation on the histology and activator enzymes of dog lungs. Heparin did seem to diminish fibrin deposition; however, sufficient histologic defects persisted to allow one to diagnose radiation pneumonitis.

Actinomycin D, 15 μg./kg., administered intravenously just prior to irradiation and for 4 subsequent days, fully protected the lungs of four 10 kg. dogs given 2,000 rads to the right hemithorax. Histologically, these lungs were completely normal and lung plasminogen activator was readily detectable in all. The mechanism of this protective action of actinomycin D is not presently understood.—*Frank J. Rigos, M.D.*

McGowan, L., and McGowan, N. E. Radiation enteritis as a complication in radiotherapy of cervical cancer. *Am. J. Digest. Dis.*, June, 1962, *7*, 523–529. (From: The Department of Obstetrics and Gynecology, Stritch School of Medicine, Loyola University, Chicago, Ill.)

The authors review the pathology, prevention, and treatment of radiation enteritis complicating radiotherapy of cervical cancer. The need for fractionated radium doses, proper placement and packing of the radium, and careful dosage calculation is pointed out. Emphasis is placed on a proper dietary program which provides good nutrition without substances which irritate or stimulate the bowel. Clinical proctosigmoiditis is four times less frequent under such a regimen.

The authors believe that most cases of acute or chronic enteritis can be treated conservatively and adequately without surgical intervention.—*George A. Miller, M.D.*

Norton, Richard A., Mahowald, Theodore A., and Monroe, Lee S. Radiation jejunitis and a choleic-acid enterolith: report of a case. *Am. J. Digest. Dis.*, July, 1962, *7*, 634–641. (Address: Dr. R. A. Norton, Scripps Clinic and Research Foundation, 476 Prospect Street, La Jolla, Calif.)

Small intestinal stricture is uncommon following roentgen therapy, and the formation of an enterolith is rare following small intestinal narrowing; yet, these two disease processes were found in the same patient.

In the case of a 70 year old widow, the history included endometrial adenocarcinoma treated in 1941 by roentgen ray and subsequent hysterectomy. The external roentgen therapy consisted of 2,000 r (in air) to each of 4 pelvic ports; 2 anterior and 2 posterior, over a 4 week period.

The patient was readmitted on January 27, 1961, for persistence of nausea and vomiting, accompanied by epigastric pain, distention, and loud borborygmus.

Laboratory data were negative. Roentgenograms of the upper gastrointestinal tract showed dilated loops

of jejunum with delayed passage of barium into the colon. No specific point of obstruction could be demonstrated. A colon study revealed no abnormality. An abdominal scout roentgenogram 2 weeks later showed several loops of small intestine distended with air.

A tentative diagnosis was made of partial intestinal obstruction from adhesive bands produced by operation or roentgen therapy.

Laparotomy was performed on February 15, 1961. No pelvic or other adhesions were noted. A hard intraluminal mass was found obstructing the jejunum about 90 cm. (3 feet) below the ligament of Treitz, with dilatation of the proximal bowel to a diameter of 5 cm. Both proximally and distally a grayish-white discoloration of the serosa and a thickening of the bowel wall were seen. A 34 cm. segment of jejunum was resected with its mesentery, and end-to-end anastomosis was completed. The gallbladder was normal to inspection and palpation, as were the liver, pancreas, and biliary tree.

Pathologic study of the resected specimen revealed the hard object to be a brown ovoid stone 2×1.6×1.2 cm. in size, weighing 2.3 gm., laminated on cross section, and with a yellow center. The bowel just below the site of the stone was narrowed to 1.0 cm. The mucosa was diffusely nodular and granular, appearing like the surface of a head of cauliflower. The changes were more marked distal to the stone.

Microscopic sections of the jejunum showed pronounced edema of the mucosa and submucosa with increase in the size of the villi. Numerous plasma cells, lymphocytes, and eosinophils were mixed through the mucosal stroma. The muscularis mucosae and submucosa showed marked edema and engorgement of lymphatics but little inflammatory infiltration. The patient recovered uneventfully and gained weight.

The enterolith was analyzed for deoxycholic acid and calcium, the main constituents of the two types of true intestinal calculi.

Radiation damage in the small intestine is seen much less frequently than in the rectum and sigmoid. In turn, jejunal injuries are more rare than ileal ones. Considering the entire digestive tract, the incidence of stricture following pelvic irradiation is not great, varying from 1.6 to 12.1 per cent in a review of 6 series of patients totaling 2,696 subjects.

The effects of ionizing radiation on the intestines consist primarily of mucosal ulceration or of fibrosis and scarring (or both). If the mucosa is not ulcerated, it may be profoundly altered, usually with mucous stasis and atrophy. Telangiectasia of veins and dilatation of the lymphatics are characteristic. Lesions may be produced in any loop of intestine that lies near the target of irradiation. The length of time between the end of therapy and surgical intervention for small intestinal symptoms averaged 26½ months in a series of 600 patients. Chronic changes in the small bowel may include thickening and edema of the entire wall, chronic inflammatory infiltration, and thickened blood vessel walls.

True enteroliths form in the intestinal lumen by precipitation of substances normally present in the chyme and are thus set apart from gallstones, foreign bodies, and stones formed from medications. Two distinct types are recognized, choleic acid stones, which form in the upper small intestine of women, and calcium stones, which form in the lower small intestine of both men and women.

The average choleic acid stone probably begins its career as a fruit stone or husk sitting in a duodenal diverticulum or other site of intestinal stasis. This nidus becomes impregnated with choleic acid, coated with it, and then the stone grows concentrically. Since it is radiolucent, the stone remains undetected unless it leaves the diverticulum and produces intestinal obstruction or, more rarely, hemorrhage.—*Stephen N. Tager, M.D.*

Byrne, Robert N., Bringhurst, Louis S., and Gershon-Cohen, J. Postoperative detection of cancer by periodic mammography of remaining breast. *Surg., Gynec. & Obst.*, Sept., 1962, *115*, 282–286. (From: Department of Radiology, Chester County Hospital, West Chester, Pa.)

Postoperative detection of cancer by periodic mammography of the remaining breast was carried out in 102 women who were referred for roentgen therapy following mastectomy. A malignant lesion was found immediately in 1 case and in 5 more cases where the patient was re-examined at intervals of 6 months. In only one instance was the lesion palpable when the radiologist referred the patient back to the surgeon.—*F. B. Markunas, M.D.*

Delory, G. E., and Penner, D. W. Parotid saliva acid phosphatase in prostatic cancer. *Brit. J. Urol.*, Sept., 1962, *34*, 331–334. (From: Winnipeg General Hospital, University of Manitoba, Winnipeg, Manitoba, Canada.)

The authors divided their patients into two groups: (1) patients with cancer of the prostate, and (2) patients with other urologic conditions. This latter group served as a control group. The analyst was not aware of the diagnosis until after the determinations of both acid phosphatase and amylase were completed.

The saliva was collected 2 hours postprandially from patients in the hospital, mostly with prostatic cancer. It was collected from the parotid gland according to the procedure of Hildes and Ferguson, stimulation being achieved by application of 1 per cent acetic acid to the tongue. The subjects were unselected.

The authors conclude from their study of the

saliva that the parotid saliva acid phosphatase and amylase levels in their series of patients with prostatic cancer and in a series of noncancerous patients did not show enough significant changes to be of any help in the diagnosis of prostatic cancer. There were 21 cases of prostatic cancer used in the parotid saliva acid phosphatase values and 61 controls in people having other urinary symptoms. In the parotid saliva amylase values there were 58 cases in the controls and 19 cases having prostatic cancer.—*Peter C. Truog, M.D.*

RADIOISOTOPES

Silverstein, Joseph N., Schwartz, Harold L., Feldman, Elaine B., Kydd, David M., and Carter, Anne C. Correlation of the red blood cell uptake of I^{131}-L-triiodothyronine and thyroxine-binding globulin capacity in man. *J. Clin. Endocrinol. & Metab.*, Oct., 1962, *22*, 1002–1006. (From: Department of Medicine, State University of New York, College of Medicine, New York City, and the Medical Service, Kings County Hospital, Brooklyn, N. Y.)

The binding of thyroid hormones to serum protein has been studied extensively. Thyroxine is bound to two serum proteins, thyroxine-binding globulin and thyroxine-binding prealbumin, as well as to serum albumin. The authors studied the simultaneous determinations of the red blood cell uptake of I^{131}-L-triiodothyronine and of the binding capacity of thyroxine-binding globulin in 108 cases in an attempt to correlate directly the cellular uptake of thyroid hormones as indicated by the red blood cells and one of the thyroxine-binding proteins. Three groups were studied: euthyroid, hyperthyroid (treated and untreated) and hypothyroid (treated and untreated). The mean thyroxine-binding globulin capacity was found to be 20.7 ± 4.8 μg./100 ml. in the normal subject as compared to that of 17.1 ± 5.0 μg./100 ml. in hyperthyroid patients and 24.3 ± 4.6 μg./100 ml. in the hypothyroid cases.

The mean binding coefficients of the red blood cell I^{131}-L-triiodothyronine uptakes were the same as those previously reported, *i.e.*, euthyroid 7.7 ± 1.5 per cent, hyperthyroid 14.8 ± 5.1 per cent, and hypothyroid 5.9 ± 1 per cent.

A significant inverse correlation was observed between the logarithm of the red cell binding coefficient and the thyroxine-binding globulin capacity in euthyroid, hyperthyroid and hypothyroid patients. It is suggested that the thyroxine-binding globulin capacity does have physiologic importance and in part, at least, regulates the cellular uptake of triiodothyronine.—*Charles W. Cooley, M.D.*

Stanbury, John B., and Janssen, M. A. The iodinated albuminlike component of the plasma of thyrotoxic patients. *J. Clin. Endocrinol. & Metab.*, Oct., 1962, *22*, 978–988. (From: Departments of Medicine, Harvard Medical School and the Massachusetts General Hospital, Boston, Mass.)

Triiodothyronine and thyroxine are the principal iodinated substances in plasma and are bound to certain proteins. The bond may be broken by treatment with butyl alcohol. They are not in peptide linkage. There is a fraction of the plasma iodine in thyrotoxic patients that is not butanol-soluble and which is present in peptide-linked iodinated amino acids. A similar substance has been found in the plasma of cases of Hashimoto's disease, in some cases of familial and sporadic goiter and also in some patients with thyroid cancer.

The butanol-insoluble iodinated fraction was studied in 20 cases of Graves' disease following the administration of therapeutic doses of I^{131} and also in 5 patients who were given 500 μc test doses of I^{131}. A method was devised to obtain this fraction free of contaminating iodinated substances. Kinetic tests were done on the fraction as well as electrophoretic studies, immunologic observations, ultracentrifuge analyses, caprylate stabilization studies, enzymatic hydrolysis and salting out studies.

The butanol-insoluble iodinated fraction was found to be similar to human serum albumin in all of the studies except that upon enzymatic hydrolysis, iodinated amino acids, principally moniodothyrosine, were released.

The authors do not know the role that the fraction plays in thyrotoxic patients or in the other mentioned thyroid disorders, but they point out that thyroid hyperplasia is common to all of the above conditions and that plasma iodoprotein may be the result of iodination of albumin that is present in, or has found its way into the hyperplastic thyroid cells.—*Charles W. Cooley, M.D.*

Baker, R. G., Rotenberg, A. D., Cederlund, J. F., and Johns, H. E. Whole body scanning in medicine. I. Physical aspects. *Canad. M. A. J.*, Aug., 1962, *87*, 367–370. (From: The Department of Medical Biophysics, University of Toronto, and Physics Division, Ontario Cancer Institute, Toronto, Ontario, Canada.)

The most practical method of measuring the distribution of a radioactive isotope within the body is to enclose a detector in a thick and heavy walled tube. The resolution or ability of the detector to distinguish adjacent sources is intensified by using a longer and smaller hole in the collimator. However, with the smaller or longer hole there is less sensitivity, so that a lower count rate is registered. One way to increase the sensitivity without loss in resolution is to use a multichannel focusing collimator with a

single large detector. Each hole looks at the same tissue portion at or near the focus, with the same resolution as a single hole, but the sensitivity is increased in proportion to the number of holes.

Most commercially available scanners have been designed for a selected region or organ of the body, and the usual scanning area is limited to 10 by 12 inches. The authors have designed a machine which will scan the whole body using a large 5 inch diameter scintillation crystal. The detector shield weighs approximately 1,500 pounds, and moves back and forth beneath the bed. The focusing collimator was constructed with 37 hexagonal tapered holes. The machine was designed to do a whole body scan in less than an hour, and the data are recorded on roentgenographic films at a choice of full, one-half or one-quarter scale.

The authors state that this is the only total body scanner in use in Canada, and is the most sensitive currently in use anywhere.—*J. L. Williams, M.D.*

Simpson, W. J. K., Rotenberg, A. D., and Baker, R. G. Whole body scanning in medicine. II. Clinical aspects. *Canad. M. A. J.*, Aug., 1962, *87*, 371–377. (From: Isotope Department, Ontario Cancer Institute, incorporating the Princess Margaret Hospital, Toronto, Ontario; and the Department of Medical Biophysics, University of Toronto, and Physics Division, Ontario Cancer Institute, Toronto, Ontario, Canada.)

Various kinds of scans were performed on 439 patients, using several types of radioactive substances.

Using I^{131}, functioning metastases were demonstrated in 11 of 26 patients with follicular or papillary thyroid cancer; in 3 of these patients the results of scans were a decisive influence in attempting radioiodine therapy.

Radioiron scans demonstrated extramedullary hematopoiesis in patients with polycythemia vera, myelofibrosis, and myelophthisic anemia.

Radiocopper studies showed abnormal concentration in the kidneys in 2 patients with Wilson's disease.

Radioactive strontium localized in bone metastases in at least 4 patients with malignant disease.

Liver and kidney scans, using I^{131} rose bengal and Hg^{203} neohydrin respectively, have been useful in the management of patients suffering from malignant disease, renal hypertension, and certain other disorders.—*J. L. Williams, M.D.*

MISCELLANEOUS

Stanton, Leonard, and Lightfoot, David A. A new ionization chamber system for regularly checking x-ray therapy machines. *Radiology*, May, 1962, *78*, 790–795. (Address: Dr. Leonard Stanton, 5525 Miriam Road, Philadelphia 24, Pa.)

A more rugged and inexpensive way of checking therapy roentgen-ray machine output is desirable. Since normally a Victoreen or similar dosimeter is not used by a technician, a simple accurate dosimeter designed specifically for the purpose is needed. Ionization chamber monitors offer advantages over both film and Victoreen type monitoring, but on modern roentgen-ray machines the small size of the monitoring chambers necessitates electronic amplification. The system described here used a special chamber design and the condenser discharge method to measure ionization current and therefore should be an improvement over the other systems.

The system consists of 3 units: an ionization chamber mounted beneath the filter of the roentgen-ray machine, a portable polystyrene capacitor-electroscope assembly, and a charger unit for the capacitor. In use the capacitor unit is charged so that the electroscope reads 0 mr. It is then plugged into the chamber in the tube housing, and the machine operates at factors as specified by calibration. The resulting "mr" reading is directly proportional to the roentgen-ray output rate, and is so reported.

Details of construction and planned changes are noted, particularly in regard to insulation. The present collector plate is constructed of cardboard coated with aquadag, as tests showed that the substitution of an aluminum foil filter increased energy-dependence effects about 50 per cent. Details of capacitor specifications are given, with the use of bendix 0–200 mr self-reading pocket dosimeters. It is felt that the current design is both reasonably accurate and stable. The limitations are understood, and it is noted that the device supplements, but is not a substitute for, calibration of the machine output in the conventional manner.—*James C. Moore, M.D.*

Spiers, F. W., and Meredith, W. J. (London, England.) Statement of dosage in megavoltage radiation therapy: Recommendations of the Faculty of Radiologists. *Clin. Radiol.*, Apr., 1962, *13*, 163–166.

The authors present a scheme for common dose statement in megavoltage therapy. It became obvious in 1960 that various centers in the United Kingdom operating 4 mev. linear accelerators had quite different statements for dose in "rads" for similar treatments. Investigation revealed that the major differences were in the concept used to describe the dose distribution. The physical factors differed only slightly at some of the centers.

PHYSICAL FACTORS RELATING TO CALIBRATION

The following recommendations are made:

(i) *Rad/roentgen conversion factor.* The values

considered here are those recommended by the International Commission of Radiological Units and Measurements (1960) and based on an energy value per ion pair in air of $W=34$ ev. It was agreed to adopt a value of 0.97 as the rad/roentgen conversion factor and to regard this as the factor for muscle or soft aqueous tissue in the energy ranges concerned. It was further agreed that the depth dose data obtained in water, together with the rad/roentgen conversion ratio, could be regarded as giving the rad dose in soft tissues.

(ii) *Dosimeter calibration.* Because medium is displaced by the ionization chamber in phantom readings, a small positive error is made. A correction factor of 0.97 to 0.98 at 4 mev. is suggested depending on the exact size and construction of the ionization chamber.

(iii) *Air spaces, bone and other factors affecting the dose distribution.* It was suggested from 2 centers that a correction of +15 per cent be made to the depth dose at points beyond lung tissue for any beam passing through a substantial portion of a lung and it was agreed that a statement should always be made of the magnitude of any such estimated correction. Since bone effect is small, modifications to the depth dose beyond the bone are not considered necessary. However, if refinements are made, approximately 5 per cent for bone in the path of the beam and 5 per cent increase from the photoelectric effect are present. If corrections are used, they should be stated. Depth dose measurements at the various centers were in good agreement.

It was concluded that, allowing for calibration and depth dose measurement, it could be expected that the physical determination of D_{50} in water would carry an error not greater than ± 3 per cent.

STATEMENT OF CLINICAL DOSE—THE MODAL DOSE

It was decided that it would be much better to have one figure as the main statement of tumor dose. This can be done with greater justification in megavoltage radiation therapy. Generally, the combination of two or three megavoltage beams produces a dose distribution with a flat plateau-like central zone falling steeply at the edges. Combinations with less sharply defined beams produce distributions with a different characteristic. It was agreed that one figure should be used as the main statement of tumor dose and that this should be the dose value, in rads to soft tissue, most commonly occurring over the volume designated as containing tumor. If the dose distribution over a grid covering the treated area (or volume) were plotted as a dose-frequency histogram, the dose value required would be the one showing the highest frequency. This is known as the modal dose because of its distribution in the dose-frequency histogram. It is also of importance to state maximum and minimum doses in the treated area, and these can be expressed as positive and negative deviations from the modal dose.

$$\text{Tumor dose} = D \text{ (rad)} \ {}^{+x}_{-y} \text{ rad.}$$

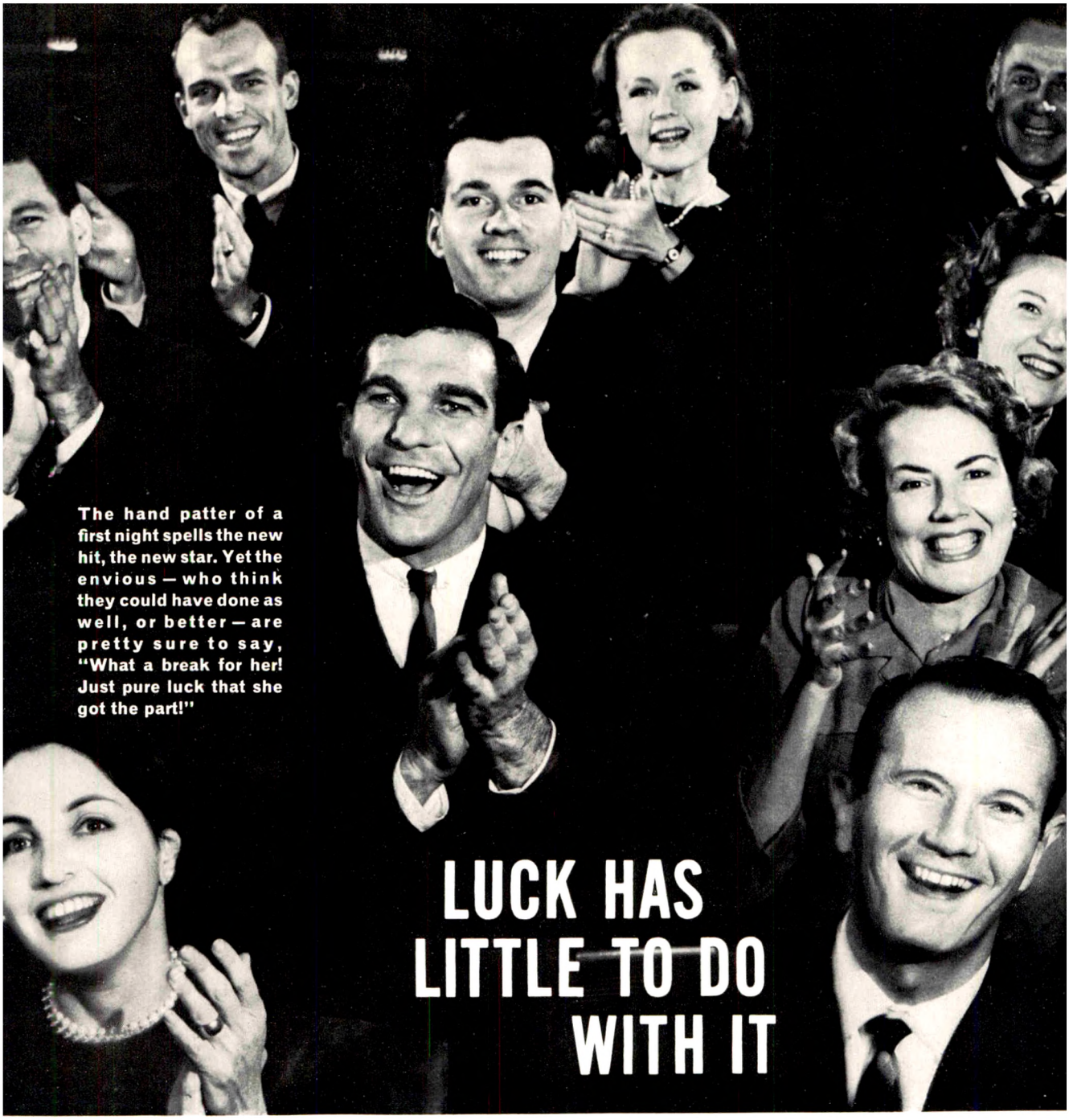
This gives a measure of the uniformity of distribution achieved in treatment planning. If there is an area of higher dosage outside the area to be treated, this should be also stated.

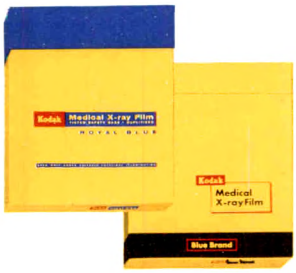
This method of dose statement was considered well suited to linear accelerator treatment at 4 mev. and also at 6 and 8 mev. Application to Co^{60} was not explored in detail but it was felt it would probably work well in fixed Co^{60} beam therapy.

APPENDICES TO THE ARTICLE

Appendix I. Two examples of uses of the modal dose in treatment volumes and histograms of the treatment area are shown.

Appendix II. Application of the dosimeter calibration factor. To obtain D, the exposure dose in roentgens at any point P, the response I in e.s.u. per 0.001293 gm. of air in an air wall chamber with equilibrium wall thickness must be corrected by a wall transmission factor f_{wall}: $D_p = I/f_{\text{wall}}$. Now, to obtain the exposure dose at a point P' completely surrounded by the medium, a correction must be used which allows for medium displacement by the chamber: $D_{p'} = (I/f_{\text{wall}}) \times f_{\text{radius}}$, where f_{radius} is a function of σ_a and σ_s which depends on radiation energy. The calibrating laboratory will give a factor F which enables I/f_{wall} to be derived from the meter reading R: $I/f_{\text{wall}} = R \times F$ roentgen. The exposure dose $D_{p'}$ at P' is thus $D_{p'} = R \times F \times f_{\text{radius}}$ roentgen. Whenever the chamber is used in a medium other than air, a correction factor f_{radius} either derived by experiment or calculated must be used. This factor for 4 mev. linear accelerator and Co^{60} is about 0.98 when water is the absorbing medium.—*George A. Kling, M.D.*





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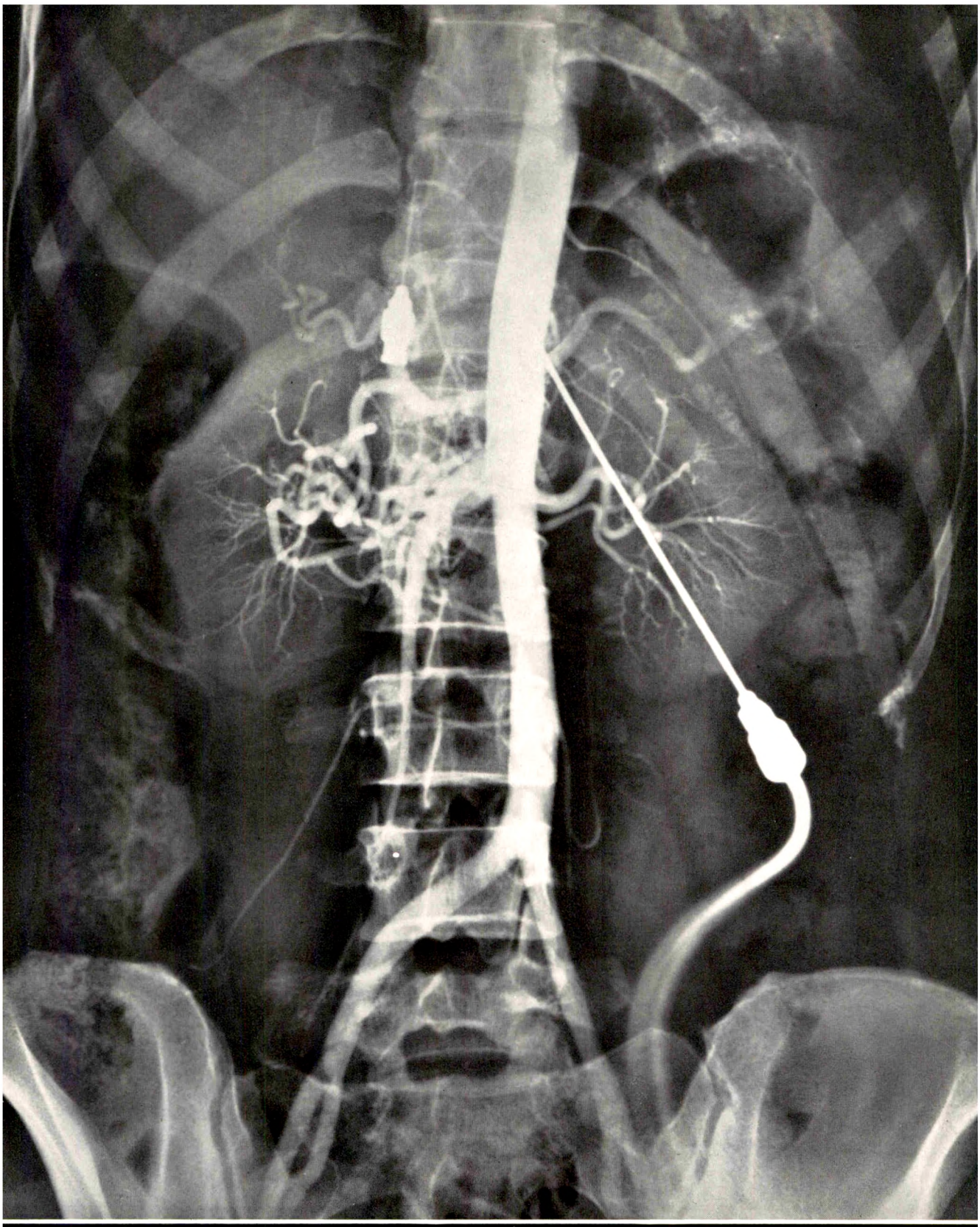
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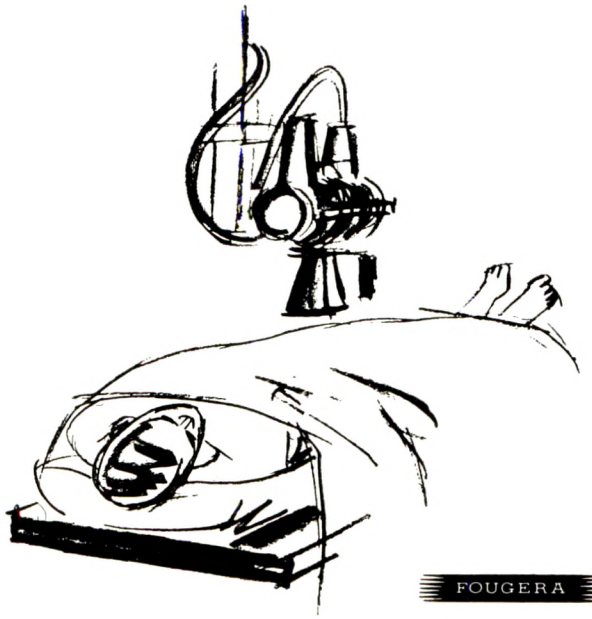
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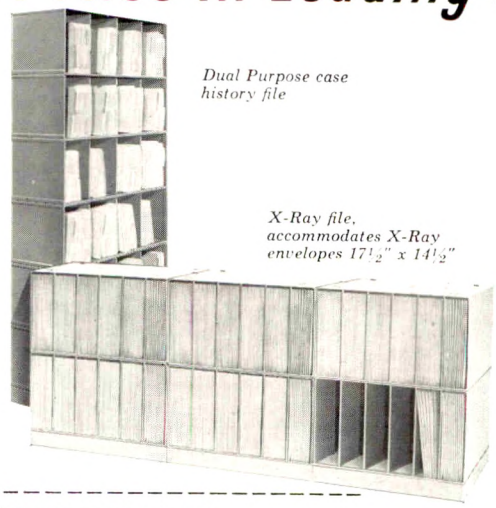
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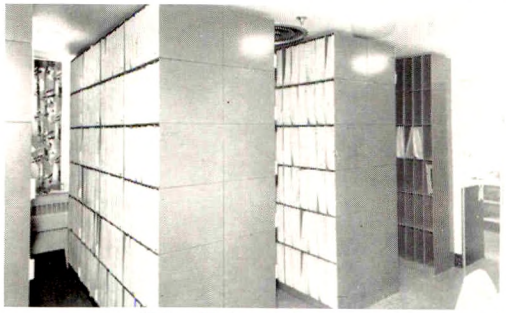
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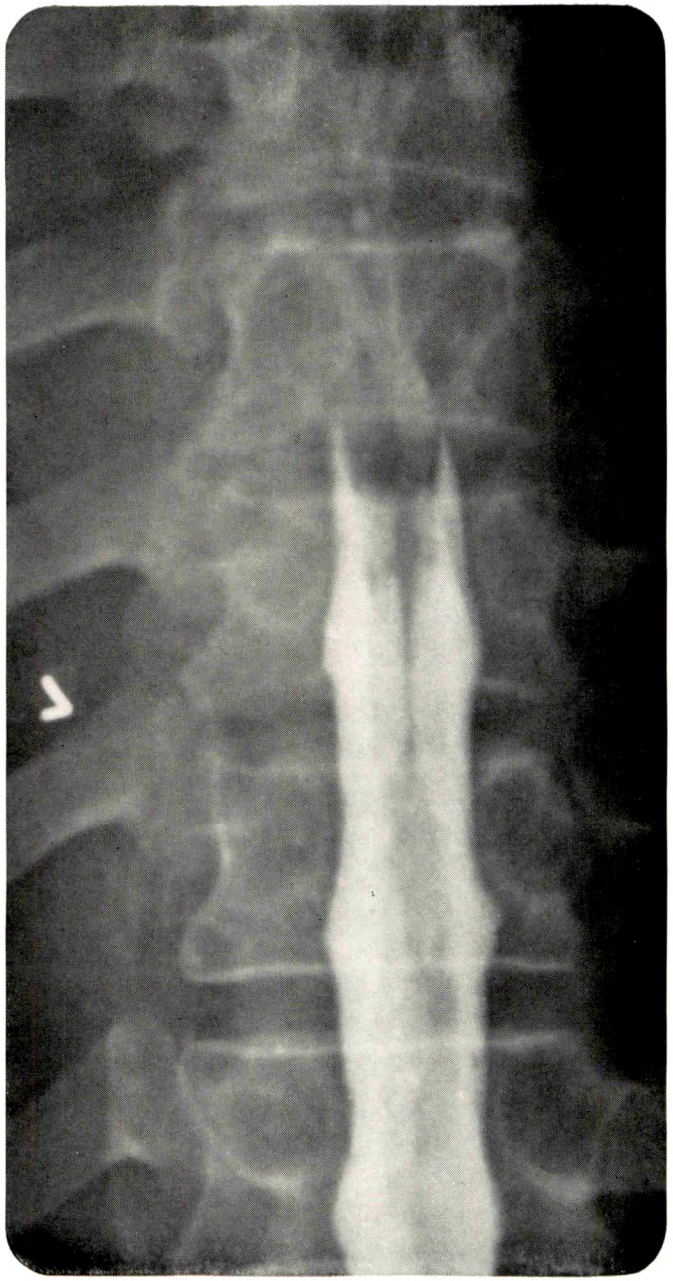
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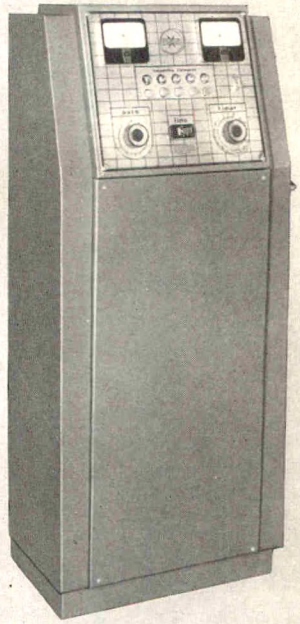
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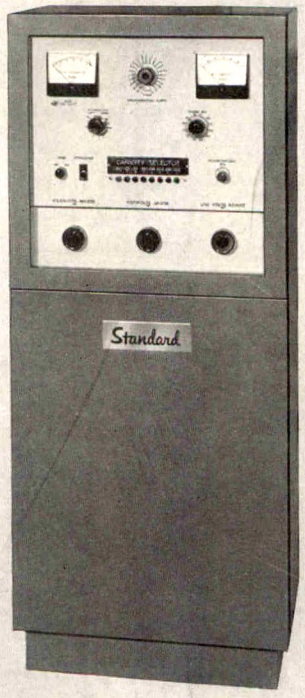
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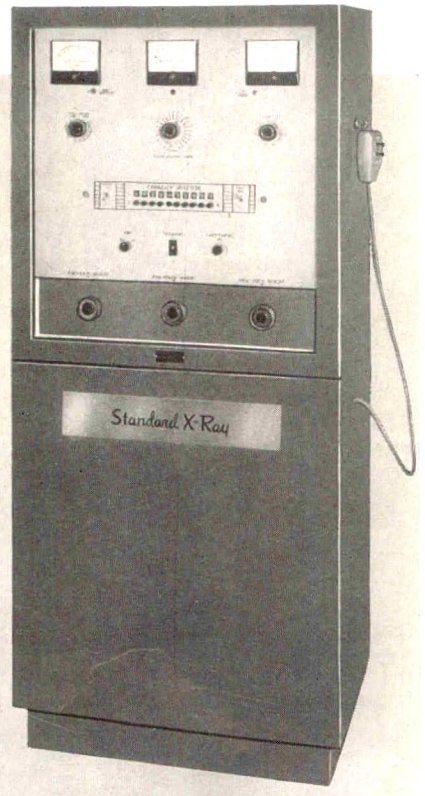
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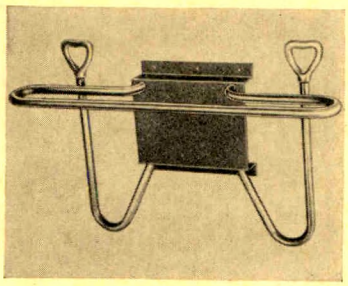
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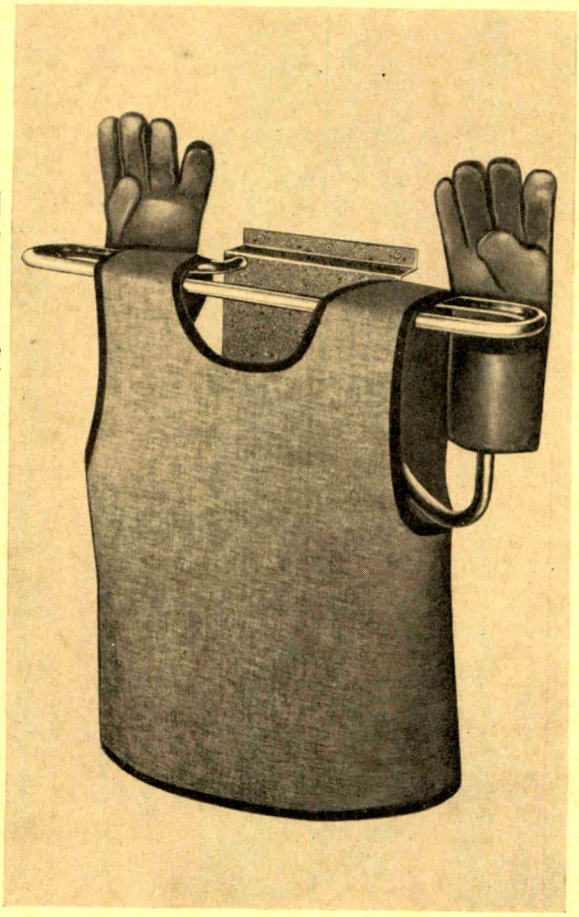
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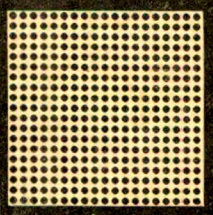
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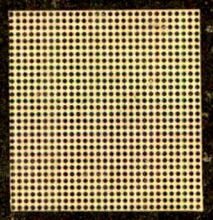
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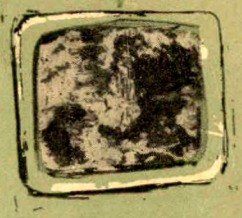


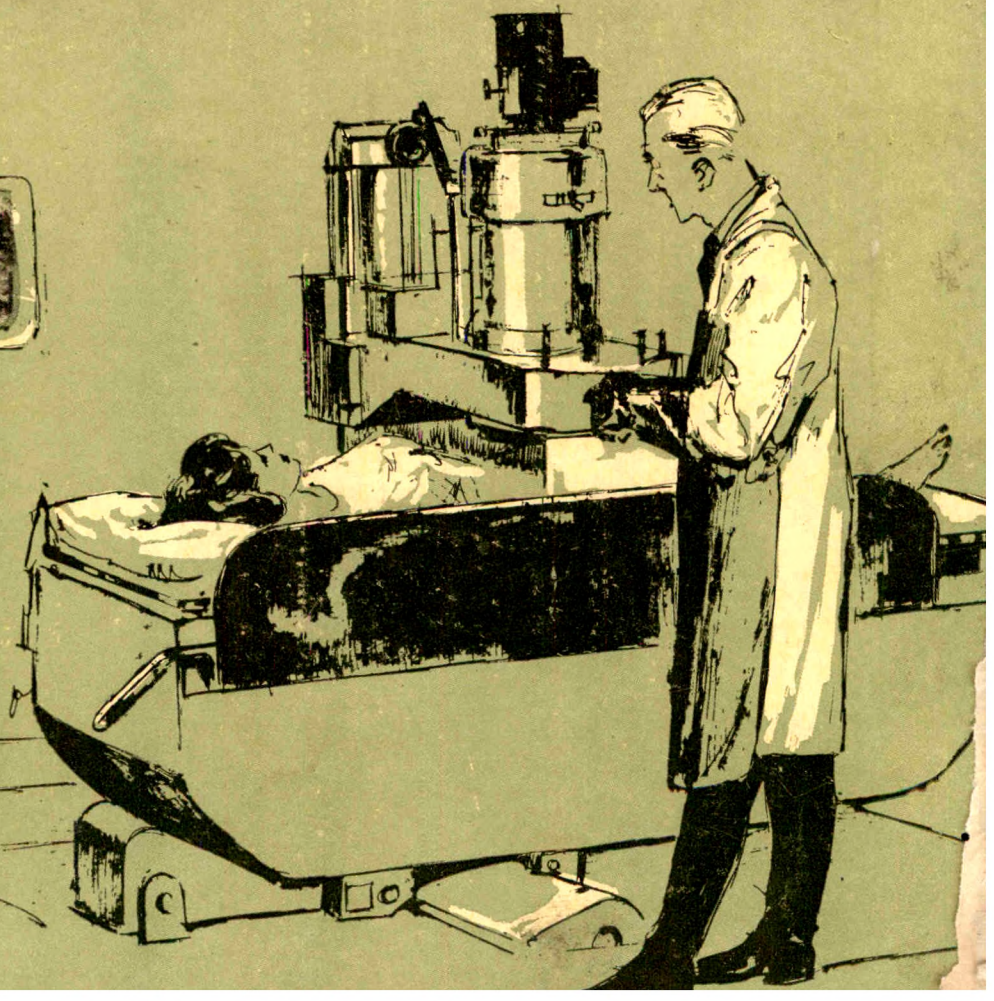
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